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Expedited synthesis of benzofuran-2-carboxylic acids via microwave-assisted Perkin rearrangement reaction

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ABSTRACT

3-Halocoumarins are readily converted into benzofuran-2-carboxylic acids via a Perkin (coumarin–benzofuran ring contraction) rearrangement reaction. This rearrangement entails initial base catalyzed ring fission. The resulting phenoxide anion then attacks a vinyl halide to produce the final benzofuran moiety. We explored this reaction under microwave reaction conditions and were able to significantly reduce reaction times as well as obtain very high yields of a series of benzofuran-2-carboxylic acid derivatives.
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Syntheses of benzofuran-2-carboxylic acid derivatives are important in the development of many biologically active molecules for potential use in the treatment of cancer as well as central nervous system disorders.[1–4] Benzofuran-2-carboxylic acids are produced from 3-halocoumarins quite readily via a Perkin (coumarin–benzofuran ring contraction) rearrangement reaction in the presence of a base such as sodium hydroxide in ethanol or methanol. This rearrangement reaction was first reported in 1870 by Perkin[5] and found to be general for 3-halocoumarins (Scheme 1).

The mechanism for the rearrangement has been proposed to involve base-catalyzed ring fission of the 3-halocoumarin, resulting in the corresponding dianion of the (*E*)-2-halo-3-(2-hydroxyphenyl)acrylic acid, followed by intramolecular nucleophilic attack on the vinyl halide by the phenoxide anion yielding the benzofuran-2-carboxylic acid as the final product. However, this proposal does not account for the lack of activation for an S_N reaction of the vinyl halide. Investigations by Dalton and Newman[6] led to another mechanistic proposal, involving initial ring fission, followed by Michael addition of methanol to the alkene, then intramolecular S_N cyclization of the alkyl halide with subsequent elimination of methanol. The mechanism for the base-catalyzed ring fission of coumarins has been studied extensively. Nucleophilic substitution of vinyl halides can proceed by a number of mechanistic pathways, more specifically those involving addition–elimination. Very insightful reaction kinetics studies by Bowden and Battah[7] supported by the determination of Hammett reaction constants propose that the Perkin rearrangement occurs in two stages. The first stage is a rapid first-order base-catalyzed ring fission that appears to occur by rate-determining addition of hydroxide anion to the carbonyl group. The Hammett reaction constant determined for the ring fission at 30.0 °C was 2.34. The second stage is a relatively slow first-order cyclization process for which the Hammett reaction constant at 60.0 °C was −3.54. Bowden and Battah went on to propose that the cyclization most likely proceeds by rate-determining fission of the carbon–halogen bond, following formation of an unstable carbanion intermediate formed by an intramolecular nucleophilic attack on the vinyl group by the phenoxide anion. This mechanistic pathway is summarized in Scheme 2.

Traditionally 3-bromocoumarins (**1**) undergo Perkin rearrangement in the presence of base at reflux for 3 h to give quantitative yield of benzofuran-2-carboxylic acids (**2**).[8] For our investigations the required 3-bromocoumarins (**1**) were prepared via microwave-assisted regioselective bromination in the presence of *N*-bromosuccinimide (NBS) as brominating agent and acetonitrile as solvent at 250 W for 5 min at 80 °C (Table 1).

We explored the Perkin rearrangement under microwave reaction conditions with variation in Power/Watts (Table 2) to obtain the best reaction conditions. We found that microwave-assisted Perkin rearrangement of 3-bromo-4-methyl-6,7-dimethoxycoumarin (**1a**) in ethanol/sodium hydroxide at either 300 W or 400 W for 5 min at 79 °C successfully yields 5,6-dimethoxy-3-methylbenzofuran-2-carboxylic acid (**2a**) in 99%. If the power was decreased to 250 W, the reaction did not go to completion during

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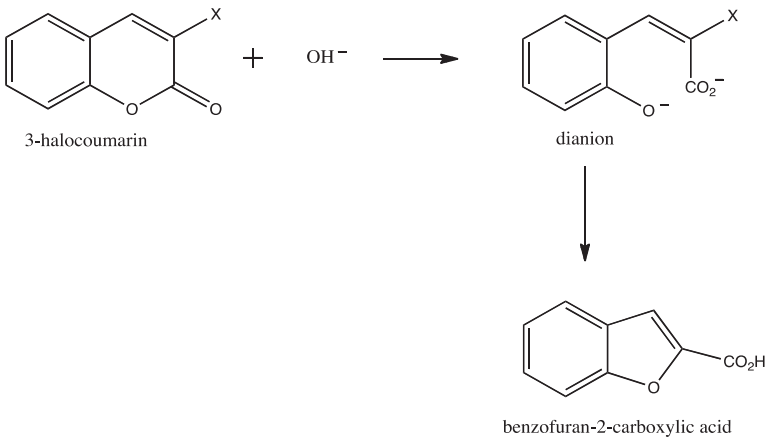


Scheme 1. Perkin (coumarin–benzofuran ring contraction) rearrangement reaction reported in 1870 by W.H. Perkin.

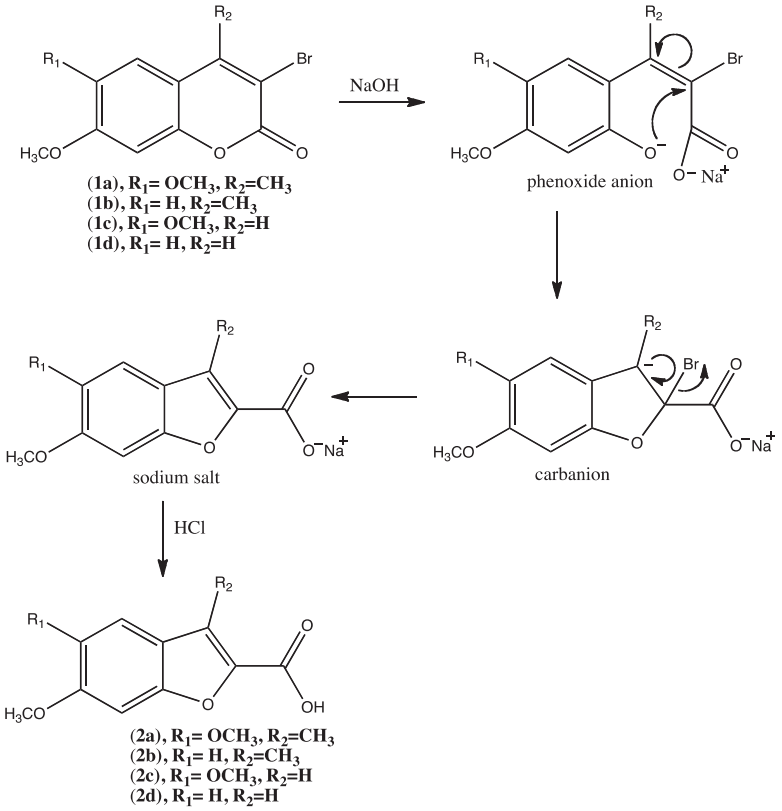
the 5-min period. Alternately, if the power was increased to 500 W, there was a slight decrease in product yield.

Using the optimized parameters of 300 W for 5 min at 79 °C, we went on to synthesize a series of benzofuran-2-carboxylic acids (**2a–d**, Table 3) in very high yield. The microwave-assisted Perkin rearrangement reaction presented here provides a more efficient synthesis of benzofuran-2-carboxylic acids from 3-bromocoumarins with a reaction time of 5 min in comparison to the traditional method with a reaction time of approximately 3 h. The rearrangement proceeds in the presence of ethanol and sodium hydroxide. During work-up hydrochloric acid was added to hydrolyze the resultant sodium salt and produce the free acid form of the corresponding benzofuran-2-carboxylic acids (**2a–d**) (Scheme 2).

General experimental

3-Bromo-4-methyl-6,7-dimethoxycoumarin (1a)

4-Methyl-6,7-dimethoxycoumarin (0.05 g, 0.227 mmol) was dissolved in acetonitrile (5 ml) in a microwave vessel. N-Bromosuccinimide (0.06 g, 0.340 mmol) was added to the mixture and the vessel inserted into the microwave at 250 W for 5 min at 80 °C. The reaction was monitored by thin layer chromatography (silica gel, 3:1 CH_2Cl_2/EtOAc). Upon completion, the reaction mixture was cooled and the resultant precipitate was collected by vacuum filtration. The crude product was then recrystallized from a mixture of CH_2Cl_2/MeOH to yield 3-bromo-4-methyl-6,7-dimeth-



Scheme 2. Perkin rearrangement of 3-bromocoumarins (**1**) to benzofuran-2-carboxylic acids (**2**) based on the mechanistic pathway reported by Bowden and Battah.

Table 1
Microwave-assisted preparation of 3-bromocoumarins (**1a**–**d**) in the presence of N-bromosuccinimide (NBS) at 250 W for 5 minutes at 80 °C

Reactant	% Yield of (**1**)
4-Methyl-6,7-dimethoxycoumarin	(**1a**), 89%
4-Methyl-7-methoxycoumarin	(**1b**), 85%
6,7-Dimethoxycoumarin	(**1c**), 83%
7-Methoxycoumarin	(**1d**), 80%

Table 2
Microwave-assisted Perkin rearrangement of 3-bromo-4-methyl-6,7-dimethoxycoumarin (**1a)**

Temperature/°C	Power/Watts	Time/min	% Yield of **(2a)**
79	250	5	Incomplete
79	300	5	99
79	400	5	99
79	500	5	90

Table 3
Microwave-assisted Perkin rearrangement of 3-bromocoumarins (**1a**–**d**) at 79 °C, 300 W, 5 min

Bromocoumarin (**1**)	Product (**2**)% Yield
(**1a**)	(**2a**), 99%
(**1b**)	(**2b**), 95%
(**1c**)	(**2c**), 99%
(**1d**)	(**2d**), 97%

oxycoumarin (**1a**, 0.060 g, 89%) as white crystals, mp 205–206 °C (lit.,[9] mp 205–206 °C).

5,6-Dimethoxy-3-methyl-benzofuran-2-carboxylic acid (2a)

3-Bromo-4-methyl-6,7-dimethoxycoumarin (**1a**) (0.05 g, 0.167 mmol) was added to a microwave vessel. Ethanol (5 ml) and sodium hydroxide (0.0201 g, 0.503 mmol) were then added to the vessel that was then sealed and inserted into the microwave for 5 min, at 300 W and at a temperature of 79 °C with stirring. The reaction was monitored by thin layer chromatography (silica gel, 3:1 CH_2Cl_2/EtOAc). Upon completion of the reaction, the mixture was concentrated on a rotary evaporator and the resultant crude product obtained was dissolved in the minimum volume of water. This solution was acidified with concentrated hydrochloric acid to pH 1 resulting in precipitation of an off-white solid which was collected by vacuum filtration and dried in an oven at 80 °C to yield 3-methyl-5,6-dimethoxybenzofuran-2-carboxylic acid (**2a**, 0.039 g, 99%), sublimes at 227–228 °C (lit.,[8] mp 228 °C); IR/cm^{-1} 3308, 1702, 1623, 1577; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.60 (3H, s, $-CH_3$), 3.95 and 4.00 (each 3H, s, $-O-CH_3$), 6.98 (1H, s), 7.09 (1H, s).

Conclusion

We have successfully performed microwave-assisted Perkin rearrangement reactions to prepare benzofuran-2-carboxylic acids (**2**) from 3-bromocoumarins (**1**) in very high yields. This expedited synthetic protocol will serve as an efficient method for the synthesis of benzofuran-2-carboxylic acids with very short reaction times in high yields.

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