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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.

Keywords

Perkin rearrangement; Halocoumarin; Benzofuran-2-carboxylic acid; Microwave; Regioselective bromination

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.^{1,2,3,4} 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 W. H. Perkin⁵ 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 Newman⁶ led to another mechanistic proposal, involving initial ring fission, followed by Michael addition of methanol to the alkene, then intramolecular S_N cyclisation 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–

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elimination. Very insightful reaction kinetics studies by Bowden and Battah⁷ 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 cyclisation process for which the Hammett reaction constant at 60.0°C was –3.54. Bowden and Battah went on to propose that the cyclisation most likely proceeds by rate-determining fission of the carbon–halogen bond, following formation of an unstable carbanion intermediate formed by 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 hours 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 250W for 5 minutes 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 300W or 400W for 5 minutes at 79°C successfully yields 5,6-dimethoxy-3-methyl-benzofuran-2-carboxylic acid (**2a**) in 99%. If the power was decreased to 250W, the reaction did not go to completion during the five-minute period. Alternately, if the power was increased to 500W, there was a slight decrease in product yield.

Using the optimized parameters of 300W for 5 minutes 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 minutes in comparison to the traditional method with a reaction time of approximately 3 hours. 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 (0.05g, 0.227mmol) was dissolved in acetonitrile (5ml) in a microwave vessel. *N*-bromosuccinimide (0.06g, 0.340mmol) was added to the mixture and the vessel inserted into the microwave at 250W for 5 minutes at 80 °C. The reaction was monitored by thin layer chromatography (silica gel, 3:1 CH₂Cl₂:EtOAc). Upon completion, the reaction mixture was cooled and the resultant precipitate collected by vacuum filtration. The crude product was then recrystallized from a mixture of CH₂Cl₂/MeOH to yield 3-bromo-4-methyl-6,7-dimethoxycoumarin (**1a**, 0.060g, 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**) (0.05g, 0.167mmol) was added to a microwave vessel. Ethanol (5ml) and sodium hydroxide (0.0201g, 0.503mmol) were then added to the vessel that was then sealed and inserted into the microwave for 5 minutes, at 300W and at a temperature of 79 °C with stirring. The reaction was monitored by thin layer chromatography (silica gel, 3:1 CH₂Cl₂: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**, 0.039g, 99%), sublimes at 227–228°C (lit.,⁸ mp 228°C); IR/cm⁻¹ 3308,1702,1623,1577; ¹H NMR (300MHz, CDCl₃): δ 2.60 (3H, s, -CH₃), 3.95 and 4.00 (each 3H, s, -O-CH₃), 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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Scheme 1.

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

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 250W 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 2Microwave-Assisted Perkin rearrangement of 3-bromo-4-methyl-6,7-dimethoxycoumarin (**1a**)

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

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

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