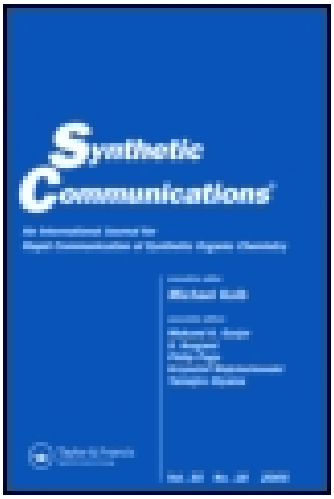

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Efficient and Convenient Method for Synthesis of Benzofuran-3-acetic Acids and Naphthafuran-acetic Acids

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EFFICIENT AND CONVENIENT METHOD FOR SYNTHESIS OF BENZOFURAN-3-ACETIC ACIDS AND NAPHTHAFURAN-ACETIC ACIDS

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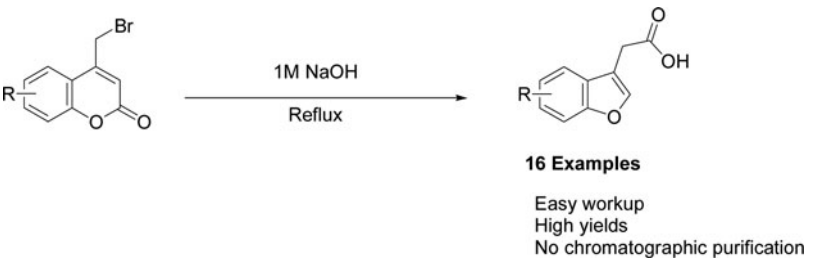
GRAPHICAL ABSTRACT



Abstract *Herein, we report an efficient and convenient method for synthesis of benzofuran-3-acetic acids and naphthafuran-acetic acids* ***5a–p*** *by the reaction of substituted-4-bromomethylcoumarins with aqueous sodium hydroxide at refluxing temperature. The obtained products are characterized by infrared,* ^{1}H *NMR,* ^{13}C *NMR, and mass spectral data. Structures* ***5a*** *and* ***5e*** *are confirmed by their single x-ray diffraction studies. The advantages of this method are good yields, easy workup, and no chromatographic purifications.*

Keywords Benzofuran; coumarin; heterocycles; Perkin; transformation

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This manuscript is dedicated to Prof. Manohar V. Kulkarni's (K.U. Dharwad) 60th birthday.

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INTRODUCTION

Benzofuran derivatives are an important class of oxygen heterocycles with a wide range of biological activities including anti-inflammatory, antitumor, cytotoxic, antimicrobial, antitubercular, antioxidant, antiplasmodial, enzyme inhibitory, hepatitis C virus (HCV) inhibitory, and human immunodeficiency virus (HIV) inhibitory activities, which have been reviewed.[1–4]

Benzofurans have been the subject of more extensive studies for the development of efficient routes for the synthesis.[5,6] The naphthofuran skeleton is present in many natural products with biological importance and its synthetic derivatives display diverse biological activities.[7] Compared to benzofurans, synthetic methods for the preparation of naphthofurans have been less reported.[8,9]

The arylalkanoic acids are a group of structurally similar compounds, many of which have interesting anti-inflammatory, analgesic, and antipyretic properties and so have been in wide clinical use for a number of years (Fig. 1).

The derivatives of 2,3-dihydro-benzofuranyl-3-acetic acids have been reported to be potent, selective, and orally bioavailable G protein-coupled receptor 40 (GPR40) and free fatty acid receptor 1 agonists (FFA1) and glucose-dependent insulinotropic agents (Fig. 2).[10–12]

It is well known that certain coumarin derivatives are transformed to other heterocycles such as pyrazoles[13] and pyrimidines[14] by their reaction with hydrazine hydrate and acetamidine or benzimidine, involving the cleavage of the lactone, respectively. The reaction of 4-formyl coumarins with phenyl hydrazine resulted in pyridazines.[15] The ring transformation of 3-halo-4-methoxycoumarins to pyrazolines has been reported.[16] The reaction of 1,2-diamines with 4-hydroxycoumarins

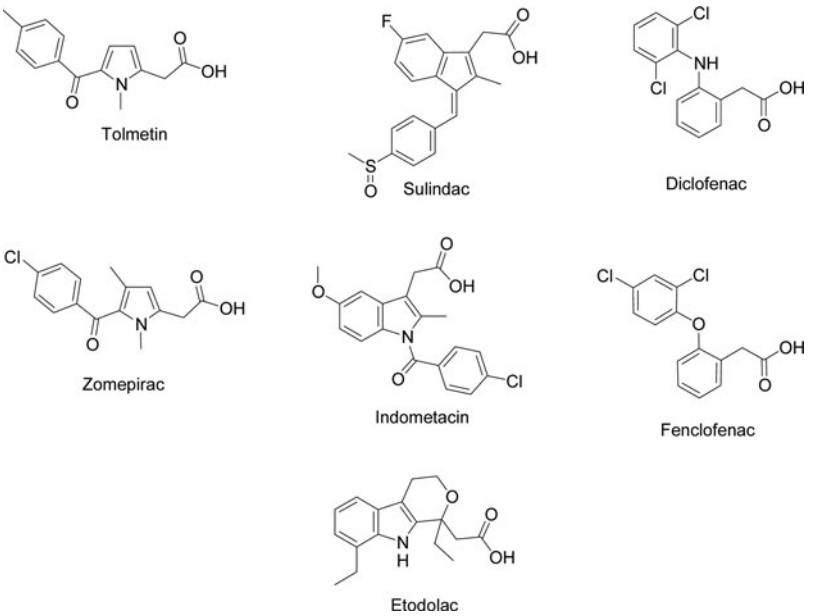


Figure 1. Biologically important arylalkanoic acids.

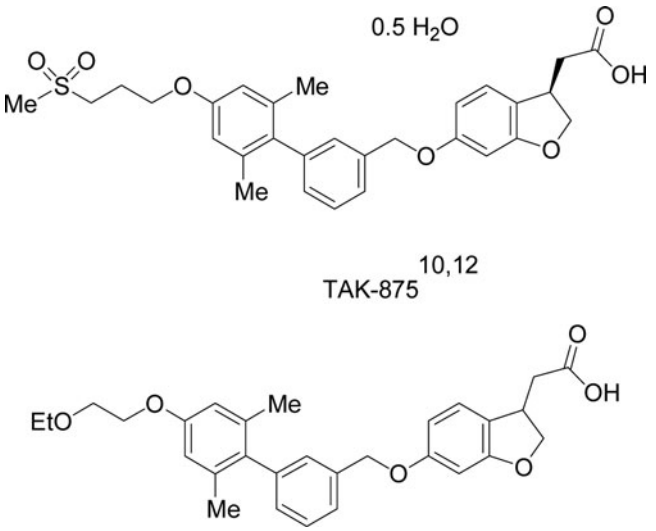


Figure 2. Structures of 2,3-dihydro-benzofuranyl-3-acetic acids as potent G protein-coupled receptor 40 agonist.[10–13]

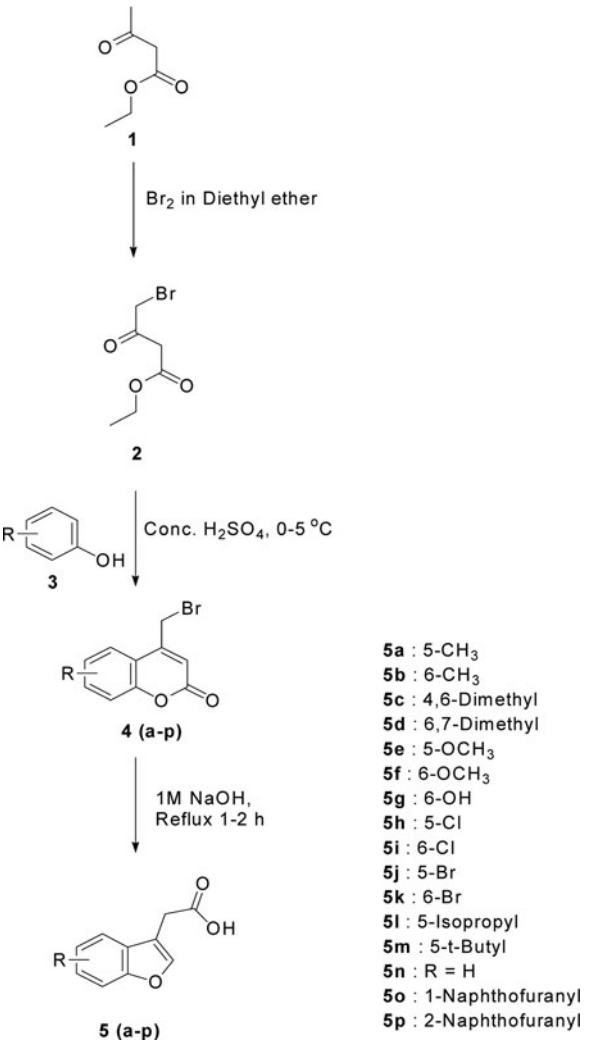
resulted in diazepine by intramolecular nucleophilic attack of the amino group onto the enolic carbon.[17] 3-Halocoumarins were readily converted into benzofuran-2-carboxylic acids via Perkin reaction by ring contraction of coumarins to benzofuran under microwave irradiation.[18]

To the best of our knowledge, premier research work on Perkin rearrangement of 4-chloromethylcoumarins to benzofuran-3-acetic acids using aqueous alkali medium was reported.[19] Later, some researchers exploited this method[20] and reported the anti-inflammatory activity of benzofuran-3-acetic acids.[21] The derivatives of naphthofuran-acetic acids were used as amino acid fluorescence labeling.[22,23]

As continuation of research work on heterocyclic transformation of 4-bromomethylcoumarins to other heterocycles[24–26] and the use of better leaving property of bromine than chlorine, herein we report a base-catalyzed Perkin rearrangement of substituted-4-bromomethylcoumarins to benzofuran-3-acetic acids and naphthofuran-acetic acids.

RESULTS AND DISCUSSION

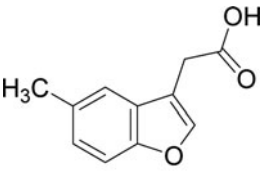
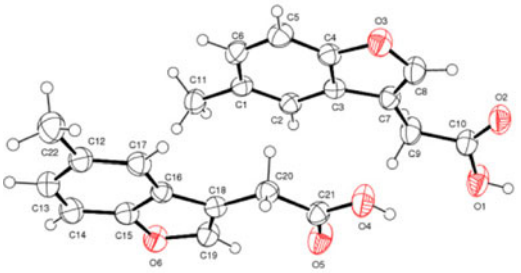
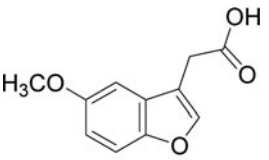
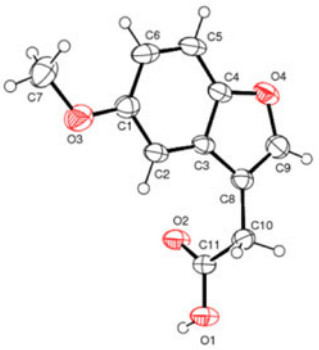
The synthesis of the benzofuran- and naphthofuran acetic acids is illustrated in Scheme 1. The required substituted-4-bromomethylcoumarins **4** were prepared by the Pechmann cyclization of substituted phenols **3** with 4-bromoethylacetoacetate **2** using sulfuric acid as the condensing agent.[27] Subsequent reaction of these substituted-4-bromomethylcoumarins **4** and 1 M sodium hydroxide was carried out at reflux, for 1–2 h, resulted in the formation of benzofuran- and naphthofuran-acetic acids **5a**–**p**. The structures of the compounds were substantiated by infrared (IR), ^{1}H NMR, ^{13}C NMR, mass spectrometry (MS), and CHN analysis. The purity of these compounds was ascertained by thin-layer chromatography (TLC) and spectral analysis (Supplementary Data).



Scheme 1. Synthesis of benzofuran- and naphthofuran acetic acids **5(a–p)**.

In the IR spectrum of the prototype, compound **5a** exhibited absorption band of carbonyl group at 1722 cm^{-1} and hydroxyl group at 3439 cm^{-1}. The ^{1}H NMR displayed two singlets at δ 2.39 and 3.65 for methyl and methylene protons, respectively. Peaks in between δ 7.11 and 7.83 affirmed the presence of four aromatic protons. The presence of carboxylic acid proton is confirmed by downfield peak at δ 12.46. The ^{13}C NMR indicated presence of methyl carbon with peak at δ 20.88, methylene carbon gave a peak at δ 28.95, and the carbonyl carbon resonated at δ 171.92. Peaks for eighteen carbons in the aromatic region from δ 110.74 to 152.92 underlined the presence of the required aromatic skeleton. Further formation of product was confirmed by mass spectra (LC-MS), which showed a molecular ion peak at m/z 191 (M+H).

Table 1. Structure and ORTEP diagram of compounds **5a** and **5e**

Structure	ORTEP diagram
 **5a**	 **CCDC No. 1401315**
 **5e**	 **CCDC No. 1401314**

To know the crystal packing, hydrogen bonding in the molecules, and orientation of acetic acid moiety with benzofuran, two compounds **5a** and **5e** were grown for single-crystal x-ray study by slow evaporation technique using an ethanol and ethyl acetate mixture. The compound **5a** exists as a dimeric form. The structures and ORTEP diagrams of compounds **5a** (CCDC No. 1401315) and **5e** (CCDC No. 1401314) are given in Table 1.

EXPERIMENTAL

The melting points were determined by open capillary method and are uncorrected. The IR spectra (KBr disc) were recorded on a Nicolet-5700 FT-IR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker 400-MHz spectrometer using dimethylsulfoxide (DMSO-d_6) as solvent and tetramethylsilane (TMS) as an internal standard. The chemical shifts are expressed in δ ppm. The mass spectra were recorded using an Agilent-Single Quartz LC-MS instrument. The elemental analysis was carried out using a Heraus CHN rapid analyzer at the University Scientific Instrumentation Centre (USIC), Karnatak University, Dharwad. The purity of the compounds was checked by TLC. All the chemicals

purchased were of analytical grade, and were used without further purification unless otherwise stated, from Sigma-Aldrich Chemicals (India) and S.D. Fine Chemicals (India).

Synthesis of (5-Methyl-benzofuran-3-yl)-acetic Acid (5a)

The substituted-4-bromomethylcoumarin **4** (10 mM) was refluxed in 1 M NaOH (100 mL) for 1-2 h (monitored by TLC). The reaction mixture was cooled and neutralized with 1 M HCl, and then the obtained product was filtered and dried. The obtained products were sufficiently pure and hence were not recrystallized.

Mp 97–98 °C (literature mp 98–100 °C),[15] yield 95%; IR (KBr, ν in cm^{-1}): 3439 (br, OH), 1722 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.39 (*s*, 3H, C5-CH_3), 3.65 (*s*, 2H, C3-CH_2), 7.11 (*d, J* = 8.4 Hz, 1H, C6-H), 7.37 (*d, J* = 0.4 Hz, 1H, C4-H), 7.42 (*d, J* = 8.4 Hz, 1H, C7-H), 7.83 (*s*, 1H, C2-H), 12.46 (*s*, 1H, COOH); ^{13}C NMR (400 MHz, DMSO-d_6): 20.88, 28.95, 110.74, 113.68, 119.71, 125.42, 127.81, 131.39, 143.44, 152.92, 171.92. LCMS *m/z:* 191 [M + 1]. Anal. calcd. for $C_{11}H_{10}O_3$: C, 69.46; H, 5.30. Found: C, 69.38; H, 5.28.

CONCLUSION

In summary, we have demonstrated a synthetic method for the transformation of substituted-4-bromomethylcoumarins to benzofuran-3-acetic acids and naphthofuran acetic acids. In particular, most reactions proceeded to completion in 1–2 h with very simple workup and direct isolation of the products in good yields without purification by either recrystallization or chromatographic assistance. The single-crystal x-ray structures of compounds **5a** and **5e** may be used to study and compare the biological activities associated with acetic acid moieties.

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SUPPLEMENTAL MATERIAL

Full experimental details, ^{1}H and ^{13}C NMR spectra, crystallographic information, and other spectral data for this article can be accessed on the publisher's website.

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