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Short Note

3-(3-Bromophenyl)-7-acetoxycoumarin

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Abstract: In natural product synthesis, the procurement of easily accessible starting materials is crucial. Chromenones and their subclass, coumarins, are a wide family of small, oxygen-containing aromatic heterocycles. Phenylcoumarins offer a particularly excellent starting point for a diverse chemical space of natural products, and thus are excellent starting materials for more complex natural products. Herein, we report an efficient synthesis of an easily accessible 3-phenylcoumarin bearing two orthogonally substitutable groups, bromine, and an acetyl-protected phenylic hydroxyl group.

Keywords: coumarin; chromenone; natural product synthesis; microwave



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1. Introduction

Coumarins are a widespread group of naturally occurring, synthetic, and semisynthetic compounds. They belong to a superfamily of heterocyclic compounds known as chromenones. A special structural group of coumarins, phenylcoumarins, are presented in nature as a subclass of flavonoids [1–3].

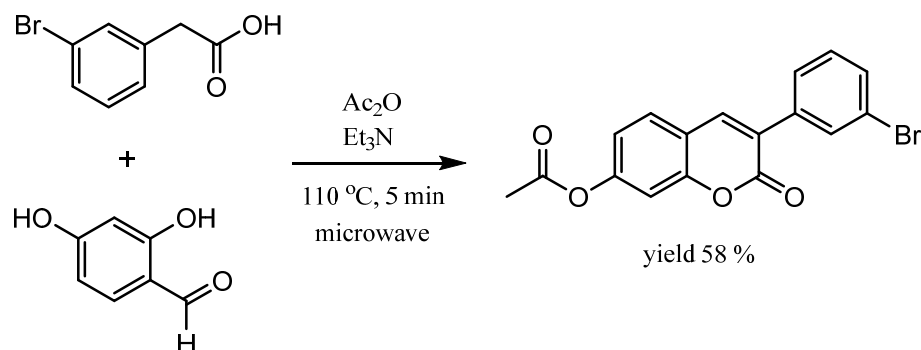
Coumarins have been studied for uses in medicinal chemistry [4,5] and metabolism studies [6] and have been utilized as dyes [7]. One important scope of the research in this field is the utilization of coumarins as building blocks of natural products. Thus, there is an urgent need for creating easily modifiable coumarin-bearing moieties. For this reason, we report herein a bifunctional coumarin containing two sites that can be easily modified. In the prepared compound, bromine at position 3 of the phenyl substituent can be altered by several different reactions, e.g., by Suzuki cross coupling [8] for C-C bond formation, via the Miyaura reaction for borylation [9], or through catalytic C-N cross-coupling, such as the Ullman reaction or Buchwald–Hartwig reaction [10]. The acetoxy group at position 7 can be deprotected into a hydroxyl group, which can also be further altered by several different reactions, e.g., esterification. It is also possible to form an additional fused five-membered ring to produce psoralen [11].

2. Results

To search for novel synthesis routes for natural products, we developed an easily accessible starting material, compound **1** (Scheme 1). The synthesis proceeded smoothly, and the purification was carried out using simple crystallization from a methanol–water solution. To avoid side reactions, the reaction time and the temperature should be kept moderate. Raising the temperature or lengthening the reaction time gave rise to the formation of side products.

In the ¹H NMR spectrum, two characteristic peaks at 7.83 ppm and 7.65 ppm show a signal from position 4 common for all 3-phenylcoumarins and a signal for 2' hydrogen next to bromine. In addition, the singlet at 2.35 ppm implicates the presence of an acetoxy group. In the ¹³C spectrum, a very characteristic carbonyl signal from lactone ring at 159.8 ppm can be

observed (please see the ^1H and ^{13}C NMR spectra in Supplementary Materials). Furthermore, only one singlet at 2.35 ppm in the ^1H NMR spectrum from the methyl group was observed, so there are no side products containing two acetoxy groups (possible bromine substitution to acetoxy group).



Scheme 1. Synthesis of 3-(3-bromophenyl)-7-acetoxycoumarin.

3. Discussion

In the present study, we have used a feasible process for the microwave-assisted synthesis of a bifunctional, easily modifiable starting material for natural product synthesis, namely, 3-(3-bromophenyl)-7-acetoxycoumarin. The method we used contained an easy purification step by crystallization with a reasonable yield.

4. Materials and Methods

4.1. General

All commercial reagents and solvents were used without further purification. ^1H and ^{13}C NMR spectra were recorded on a 600 MHz Bruker Avance III HD spectrometer equipped with CryoProbe operating at 600.2 and 150.9 MHz, respectively. CDCl_3 was used as solvent and tetramethylsilane (TMS) as an internal standard for calibrating the chemical shifts. High-resolution mass spectrum (HRMS) was recorded on mass spectrometer (Q Exactive Classic, Thermo Scientific, Bremen, Germany) using electrospray ionization (ESI) in the positive mode. The synthesis was carried out using microwave synthesizer (Biotage[®] Initiator+ Microwave System with Robot Eight, Uppsala, Sweden).

4.2. Synthesis of 3-(3-bromophenyl)-7-acetoxycoumarin

In a 5 mL microwave vial containing 375 μL of triethylamine and 375 μL of acetic anhydride, 3-bromophenylacetic acid (325 mg; 1.5 mmol) and 2,4-dihydroxybenzaldehyde (209 mg; 1.5 mmol) were added, mixed for 5 min, and then heated to 110 $^\circ\text{C}$ for 5 min with 2 min of pre-stirring in a microwave synthesizer applied. MeOH (5 mL) was added into reaction mixture, mixed for 5 min, and then water was added to make $\text{H}_2\text{O}/\text{MeOH}$ (2:8) solution. Precipitate was filtered and $\text{H}_2\text{O}/\text{MeOH}$ (1:1) solution was used for washing the precipitate. Crystallization of the filtered and air-dried precipitate from $\text{H}_2\text{O}/\text{MeOH}$ (2:8) solution after drying in vacuo yielded (313 mg, 58 %) the titular compound as a light red powder. M.p. 164–167 $^\circ\text{C}$.

^1H NMR δ 7.83 (t, $J = 1.8$ Hz, 1H), 7.81 (s, 1H), 7.67–7.64 (m, 1H), 7.57–7.53 (m, 2H), 7.33 (t, $J = 7.9$ Hz, 1H), 7.16 (d, $J = 1.9$ Hz, 1H), 7.09 (dd, $J = 2.1, 8.4$ Hz, 1H), 2.35 (s, 1H). ^{13}C NMR δ 168.7, 159.8, 154.2, 153.2, 139.8, 136.5, 131.9, 131.4, 130.0, 128.8, 127.2, 126.3, 122.5, 118.7, 117.2, 110.1, 21.2. HRMS m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{17}\text{H}_{11}\text{O}_4\text{Br}$ 358.9919; found: 358.9916.

5. Conclusions

In this study, we have developed an easily accessible starting material for natural product syntheses using a simple and efficient microwave-assisted reaction.

Supplementary Materials: The following are available online, ^1H and ^{13}C NMR spectra of the title compound.

Author Contributions: Conceptualization, J.M.T.; performing synthesis, L.P.N.; writing—original draft preparation, J.M.T.; writing—review and editing, P.A.T., L.P.N. and J.M.T.; supervision, P.A.T. and J.M.T. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

References

1. Bouhaoui, A.; Eddahmi, M.; Dib, M.; Khouili, M.; Aires, A.; Catto, M.; Bouissane, L. Synthesis and biological properties of coumarin derivatives. A review. *ChemistrySelect* **2021**, *6*, 5848–5870. [[CrossRef](#)]
2. Carneiro, A.; João, M.; Uriarte, E.; Lourdes, S. Trending topics on coumarin and its derivatives in 2020. *Molecules* **2021**, *26*, 501–515. [[CrossRef](#)] [[PubMed](#)]
3. Matos, M.J.; Uriarte, E.; Santana, L. 3-Phenylcoumarins as a Privileged Scaffold in Medicinal Chemistry: The Landmarks of the Past Decade. *Molecules* **2021**, *26*, 6755. [[CrossRef](#)] [[PubMed](#)]
4. Hassan, R.; Mohi-ud-din, R.; Sabreen, S.; Banday, N.; Maqbool, M. Coumarin Derivatives as Potential Anti-inflammatory Agents for Drug Development. In *Frontiers in Natural Product Chemistry Volume 8*, 1st ed.; Atta-Ur-Rahman, F.R.S., Ed.; Bentham Science Publisher: Sharjah, United Arab Emirates, 2021; Volume 8, pp. 213–238. [[CrossRef](#)]
5. Timonen, J.M.; Nieminen, R.M.; Sareila, O.; Goulas, A.; Moilanen, L.J.; Haukka, M.; Vainiotalo, P.; Moilanen, E.; Aulaskari, P.H. Synthesis and anti-inflammatory effects of a series of novel 7-hydroxycoumarin derivatives. *Eur. J. Med. Chem.* **2021**, *46*, 3845–3850. [[CrossRef](#)] [[PubMed](#)]
6. Raunio, H.; Pentikäinen, O.; Juvonen, R.O. Coumarin-Based Profluorescent and Fluorescent Substrates for Determining Xenobiotic-Metabolizing Enzyme Activities In Vitro. *Int. J. Mol. Sci.* **2020**, *21*, 4708. [[CrossRef](#)] [[PubMed](#)]
7. Elgemeie, G.H.; Reham, A.M. Microwave synthesis of fluorescent and luminescent dyes (1990–2017). *J. Mol. Struct.* **2018**, *1173*, 707–742. [[CrossRef](#)]
8. Enríquez-Palacios, E.; Arbeloa, T.; Bañuelos, J.; Bautista-Hernández, C.I.; Becerra-González, J.G.; López-Arbeloa, I.; Peña-Cabrera, E. Ready Access to Molecular Rotors Based on Boron Dipyrromethene Dyes-Coumarin Dyads Featuring Broadband Absorption. *Molecules* **2020**, *25*, 781. [[CrossRef](#)] [[PubMed](#)]
9. Tianzhi, Y.; Zeyang, Z.; Yanjun, B.; Yuling, Z.; Xiaoxiao, L.; Hui, Z. Investigation of novel carbazole-functionalized coumarin derivatives as organic luminescent materials. *Dyes Pigments* **2017**, *147*, 260–269. [[CrossRef](#)]
10. Sovari, S.N.; Vojnovic, S.; Bogojevic, S.S.; Crochet, A.; Pavic, A.; Nikodinovic-Runic, J.; Zobi, F. Design, synthesis and in vivo evaluation of 3-aryl coumarin derivatives of rhenium(I) tricarbonyl complexes as potent antibacterial agents against methicillin-resistant *Staphylococcus aureus* (MRSA). *Eur. J. Med. Chem.* **2020**, *205*, 112533. [[CrossRef](#)] [[PubMed](#)]
11. Timonen, J.M.; Vuolteenaho, K.; Leppänen, T.; Nieminen, R.M.; Aulaskari, P.; Jänis, J.; Vainiotalo, P.; Moilanen, E. Synthesis of Novel Anti-inflammatory Psoralen Derivatives—Structures with Distinct Anti-Inflammatory Activities. *J. Heterocycl. Chem.* **2018**, *55*, 2590–2597. [[CrossRef](#)]