chemistry proceedings

MDPI

Proceeding Paper

A Straightforward and Efficient Approach for the Synthesis of 3-Cyano-Coumarine Derivatives †

Asmaa Kebaili [1,2,*], Fatima Belhadj [1,3], Zahira Kibou [1,2], Julio A. Seijas [4], M. Pilar Vazquez Tato [4] and Noureddine Choukchou-Braham [1]

[1] Laboratoire de Catalyse et Synthèse en Chimie Organique, Faculté des Sciences, Université de Tlemcen, BP 119, 13000 Tlemcen, Algeria; fbelhadj88@yahoo.fr (F.B.); zahirakibou@yahoo.fr (Z.K.); nourredine.choukchoubraham@gmail.com (N.C.-B.)
[2] Faculté des Sciences et de la Technologie, Université d'Ain Témouchent, BP 284, 46000 Ain Témouchent, Algeria
[3] Faculté de Médecine, Université d'Oran 1, BP 1510, 31000 ElMenaouar Oran, Algeria
[4] Departamento de Quimica Orgànica, Facultad de Ciencias, Universidad de Santiago de Compostela, A da, Alfonso X EL Sabio s/n, 27002 Lugo, Spain; julio.seijas@usc.es (J.A.S.); pilar.vazquez.tato@usc.es (M.P.V.T.)
* Correspondence: kebailiasmaa97@gmail.com
† Presented at the 28th International Electronic Conference on Synthetic Organic Chemistry (ECSOC 2024), 15–30 November 2024; Available online: https://sciforum.net/event/ecsoc-28.

Abstract: Oxygen heterocycles represent a significant category of organic molecules that are abundant in nature, highlighting their importance in scientific research due to their diverse application across various fields. Coumarins in particular, comprise a wide range of compounds known for their extensive biological activities, making them invaluable in medicine, pharmacology, cosmetics, and the food industry. The biological effects and potential applications of coumarins are closely tied to their specific chemical structures. As a result, researchers frequently engage in the synthesis of coumarin derivatives to explore their varied uses. In this context, we focus on the synthesis of 3-cyano-coumarin and its derivatives. This study introduces a simple synthesis method that enables the efficient and accessible production of these structures under mild, environmentally friendly conditions, yielding excellent results.

Keywords: organic synthesis; oxygen heterocycles; 3-cyano-coumarine derivatives

Citation: Kebaili, A.; Belhadj, F.; Kibou, Z.; Seijas, J.A.; Tato, M.P.V.; Choukchou-Braham, N. A Straightforward and Efficient Approach for the Synthesis of 3-Cyano-Coumarine Derivatives. *Chem. Proc.* **2024**, *6*, x. https://doi.org/10.3390/xxxxx

Academic Editor(s): Name

Published: date

1. Introduction

Heterocyclic compounds constitute the largest and most diverse group of organic compounds. Their numbers. Their numbers are growing rapidly due to ongoing research and advancements in synthesis technique [1,2]. These compounds are significant across various scientific disciplines, including medicinal chemistry and biochemistry. Numerous heterocyclic compounds are currently known [3,4]. Mainly oxygen heterocyclic compounds [5,6], they are a vital class of organic molecules found abundantly in nature, highlighting their importance in scientific research due to their diverse applications across multiple fields [7]. Extensive research has focused on the development of new molecular composite materials, numerous organic synthesis protocols that have a wide range of applications in the chemical sciences [8,9]. Numerous oxygen heterocyclic compounds found in nature possess both physiological and pharmacological properties, and they are integral to many important biological molecules [10,11], particularly coumarins [12].

Coumarins comprise a diverse range of compounds recognized for their wide spectrum of biological activities, including antioxidant, anticonvulsant, and antitumor, anti-inflammatory, and antimicrobial properties [13,14]. This makes them invaluable in fields such as medicine, pharmacology, cosmetics, and the food industry. The biological effects and potential applications of coumarins are closely tied to their unique chemical

structures. The broad range of applications and growing interest in coumarins as a key heterocycle have motivated us to explore recent advancements in their synthesis [15,16].

In this context, we are interested on the synthesis of 3-cyano-coumarin and its derivatives (Figure 1). This study introduces a simple synthesis method that enables the efficient and accessible production of these structures under mild, environmentally friendly conditions, achieving excellent yields.

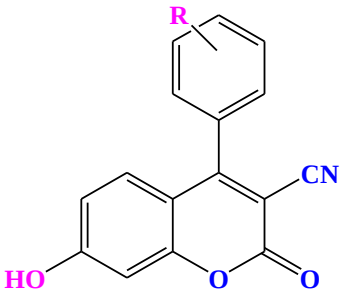


Figure 1. General structure of 3-cyano-coumarin derivatives.

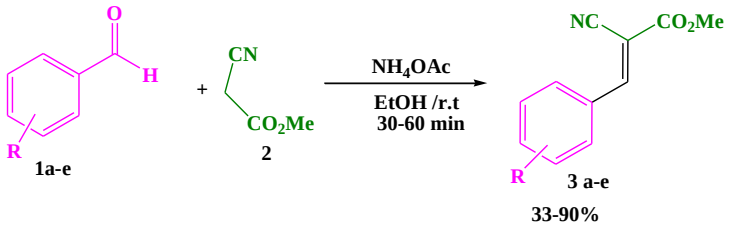
2. Results and Discussion

In this work, we report the two-step synthesis of 3-cyano-coumarin derivatives, outlined as follows:

*2.1. Alkenes Synthesis **3a–e***

The initial step in our synthetic approach is the synthesis of variuos alkenes (**3a–e**) by reacting substituted aromatic aldehydes (**1a–e**) with methyl cyanoacetate (**2**) and stirring the mixture at room temperature for 30 to 60 min, we obtained the desired products In good yields (Table 1).

Table 1. Synthesis of Alkynes.



Entry	R	Yields (%)
3a	H	33
3b	4-Cl	73
3c	4-F	79
3d	3-CH_3	59
3e	3,4,5 tri-OMe	90

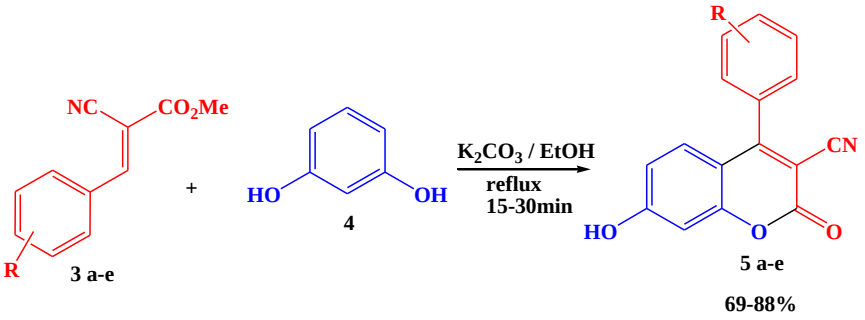
The structure of the synthesized compounds **3a–e** was confirmed by spectral analysis; the IR spectra (KBr, ν, cm^{-1}) showed the appearance of (CN) at 2215–2222 cm^{-1}, (C=C) at 1575–1603 cm^{-1}, and (C=O) at 1719–1736 cm^{-1}, the ^1H NMR ($CDCl_3$, δ, ppm) showed the appearance of C-H stretch at 8.16–8.80 ppm, CH_3 stretch at 2.45 ppm, and H_{Ar} at 7.16–7.97 ppm, and finally O-CH3 stretch at 3.85–4.04 ppm.

*2.2. Synthesis of 3-Cyano-Coumarins Derivatives **5a–e***

We synthesized a series of 3-cyano-coumarin derivatives (**5a–e**) using the previously synthesized alkynes (**3a–e**) in combination with resorcinol (**4**). This reaction was

conducted at reflux with K_2CO_3 as catalyst and ethanol as the solvent for 15 to 30 min. This strategy resulted in the formation of 3-cyano-coumarin derivatives in excellent yields (Table 2).

Table 2. Synthesis of 3-cyano-coumarin derivatives.



Entry	R	Yields (%)
3a	**H**	**71**
3b	**4-Cl**	**88**
3c	**4-F**	**69**
3d	**3-CH_3**	**73**
3e	**3,4,5 tri-OMe**	**77**

The synthesized compounds **5a–e** was confirmed by spectroscopic analysis; the IR spectra (KBr, ν, cm^{-1}) showed the appearance of (CN) at 2202–2208 cm^{-1}, and (C=O) at 1683–1684 cm^{-1}, and (OH) at 3218–3234.

3. Experimental Procedures

*3.1. General Synthesis of Alkynes Derivatives **3a–e***

An equimolar mixture of methyl cyanoacetate (0.02 mol) with different derivatives of aromatic aldehydes (0.02 mol) in the presence of 5 mL EtOH as solvent and catalytic amount of NH_4OAc at room temperature for 30 to 60 min, the progress of the reaction is monitored by TLC, the solid formed washed and filtered by diethyl ether and some drop of ethanol to afford the desired product in good yields (33–90%).

*3.2. General Synthesis of 3-Cyano-Coumarin Derivatives **5a–e***

The products (**5a–e**) were prepared using (0.02 mol) of Alkynes **3a–e** with (0.02 mol) of resorcinol **4** in the presence of a catalytic amount of K_2CO_3 and about 5 mL of ethanol as a solvent the reaction mixture was stirred and refluxed at 60 °C for 15 to 30 min according to TLC, the formed solid after cooling was collected by filtration and washed with diethyl ether and ethanol. The required products were obtained with excellent yields (69–88%).

4. Conclusions

We have successfully developed a simple, rapid and efficient synthesis route for 3-cyano-coumarin derivatives. This process offers several advantages, including mild reaction condition, straightforward reactants, and excellent yields.

Author Contributions:

Funding: The study is supported by the General Directorate for the Scientific Research and Technological Development (DGRSDT), and the Universities of Tlemcen and Ain Temouchent.

Institutional Review Board Statement:

Informed Consent Statement:

Data Availability Statement:

Acknowledgments: The authors wish to thank the General Directorate for Scientific Research and Technological Development (DGRSDT), the Universities of Tlemcen and Ain Temouchent for the financial support.

Conflicts of Interest: The authors declare no conflict of interest, financial or otherwise.

References

1. Arora, P.; Arora, V.; Lamba, H.; Wadhwa, D. Importance of heterocyclic chemistry: A review. *Int. J. Pharm. Sci. Res.* **2012,** *3*, 2947.
2. Bhattacherjee, D.; Zyryanov, G.V.; Das, P. Recent advances in the synthetic approaches to 2-pyridones (microreview). *Chem. Heterocycl. Compd.* **2020,** *56*, 1152–1154. https://doi.org/10.1007/s10593-020-02789-z.
3. Kabir, E.; Uzzaman, M. A review on biological and medicinal impact of heterocyclic compounds. *Results Chem* **2022**, *4*, 100606. https://doi.org/10.1016/j.rechem.2022-100606.
4. Asmaa, K.; Fatima, B.; Zahira, K.; Noureddine, C.-B. Ten Years of Progress in the Synthesis of 2-Pyridone Derivatives via Three/Four Component Reaction. *Mini-Rev. Org. Chem.* **2023,** *20*, 358–371. https://doi.org/10.2174/1570193X19666220519090636.
5. Patrusheva, O.S.; Volcho, K.P.; Salakhutdinov, N.F. Synthesis of oxygen-containing heterocyclic compounds based on monoterpenoids. *Russ. Chem. Rev*. **2018,** *87*, 771. https://doi.org/10.1070/RCR4810.
6. Cafeo, G.; Satira, A.; Russo, M.; Mondello, M.; Dugo, P. Determination of Oxygen Heterocyclic Compounds in Foods Using Supercritical Fluid Chromatography–Tandem Mass Spectrometry. *Foods* **2023,** *12*, 3408. https://doi.org/10.3390/foods12183408.
7. Vijayakumar, B.; Ranga Rao, G. PWA/montmorillonite K10 catalyst for synthesis of coumarins under solvent-free conditions. *J. Porous Mater.* **2012,** *19*, 233–242. https://doi.org/10.1007/s10934-011-9465-x.
8. Abdou, M.M. 3-Acetyl-4-hydroxycoumarin: Synthesis, reactions and applications. *Arab. J. Chem.* **2017,** *10*, S3664–S3675. https://doi.org/10.1016/j.arabjc.2014.04.005.
9. Slimani, I.; Hamzaoui, S.; Mansour, L.; Harrath, A.H.; Hamdi, N. One-pot, simple and efficient synthesis of novel bioactive 4-aryl-1, 2-dihydro-6-(4-hydroxy-2-oxo-2H-chromen-3-yl)-2-oxopyridin-3-carbonitriles via multi-component approach. *J. King Saud Univ. Sci.* **2020,** *32*, 1212–1217. https://doi.org/10.1016/j.jksus.2019.11.02.
10. Siziani, D.; Ziani, B.E.C.; Abdi, Y.; Bensouilah, N.; Boutemeur-Kheddis, B.; Ziani, C.; Boukkena, L.; Hamdi, M.; Talhi, O.; Bachari, K. Multicomponent synthesis of pyranonicotinonitrile and chromene-3-carbonitrile: Studies on bioactivities and molecular docking. *J. Mol. Struct.* **2022,** *1264*, 13236. https://doi.org/10.1016/j.molstruc.2022.133236.
11. Abu El-Azm, F.S.; El-Shahawi, M.M.; Elgubbi, A.S.; Madkour, H.M. Synthesis of new benzo [f] chromene-based heterocycles targeting anti-proliferative activity. *J. Iran. Chem. Soc.* **2021,** *18*, 1081–1092. https://doi.org/10.1007/s13738-020-02092-w.
12. Zeydi, M.M.; Kalantarian, S.J.; Kazeminejad, Z. Overview on developed synthesis procedures of coumarin heterocycles. *J. Iran. Chem. Soc.* **2020,** *17*, 3031–3094. https://doi.org/10.1007/s13738-020-01984-1.
13. Rezayati, S.; Sheikholeslami-Farahani, F.; Rostami-Charati, F.; Abad, S.A.S. One-pot synthesis of coumarine derivatives using butylenebispyridinium hydrogen sulfate as novel ionic liquid catalyst. *Res. Chem. Intermed.* **2016,** *42*, 4097–4107. https://doi.org/10.1007/s11164-015-2261-5.
14. Bardasov, I.; Alekseeva, A.Y.; Malyshkina, N.; Ershov, O.; Surazhskaya, M.; Grishanov, D. New synthesis of 4-alkyl-3-cyanocoumarins. *Russ. J. Org. Chem.* **2016,** *52*, 983–986. https://doi.org/10.1134/S1070428016070101.
15. Molnar, M.; Lončarić, M.; Kovač, M. Green chemistry approaches to the synthesis of coumarin derivatives. *Curr. Org. Chem.* **2020,** *24*, 4–43. https://doi.org/10.2174/1385272824666200120144305.
16. Bardasov, I.; Malyshkina, N.; Alekseeva, A.Y.; Ershov, O.; Timrukova, D.; Grigor'eva, A. Synthesis and optical properties of new coumarin derivatives based on 2-(2-chlorobenzylidene) malononitrile. *Russ. J. Org. Chem.* **2017,** *53*, 47–50. https://doi.org/10.1134/S1070428017010080.