chemistry proceedings

MDPI

Proceedings Paper

Modified Algar-Flynn-Oyamada Reaction for The Synthesis of 3-Hydroxy-2-styryl-chromen-4-ones under Solvent-Free Conditions †

Dinesh Kumar

Department of Chemistry, Kishan Lal Public College, Rewari 123401, India; dksharma_84@rediffmail.com

† Presented at the 26th International Electronic Conference on Synthetic Organic Chemistry; Available online: https://ecsoc-26.sciforum.net/.

Abstract: A simple and efficient condition for Algar-Flynn-Oyamada reaction for the synthesis of 3-hydroxy-2-styryl-chromen-4-ones involving grinding of different 1-(2′-hydroxy-phenyl)-5-aryl-penta-2,4-dien-1-ones with UHP (urea-hydrogen peroxide), pulverized potassium hydroxide and few drops of ethanol at room temperature under solvent-free conditions has been described. A faster reaction and higher yields compared to the conventional methods are the advantages of present protocol. The structure of the synthesized compounds was identified from their spectral data (IR, ^{1}H-NMR).

Keywords: Algar-Flynn-Oyamada reaction; 3-hydroxy-2-styryl-chromen-4-ones; 1-(2-hydroxy-phenyl)-5-aryl-penta-2,4-dien-1-ones; UHP; solvent-free conditions

Citation: Kumar, D. Modified Algar-Flynn-Oyamada Reaction for The Synthesis of 3-Hydroxy-2-styryl-chromen-4-ones under Solvent-Free Conditions. *Chem. Proc.* **2022**, *4*, x. https://doi.org/10.3390/xxxxx

Academic Editor: Julio A. Seijas

Published: 15 November 2022

1. Introduction

Styryl chromones are an important class of flavonoid family possesses various biological activities, such as antioxidant, anti-inflammatory, antimicrobial, antitumor, and neuroprotective activities [1–7]. Only nine derivatives of styrylchromones have been isolated from some natural sources so far, which include cryptophycean alga, *Chrysophaeum taylori*, *Imperata cylindrica*, Chinese eaglewood, *Platanus x acerifolia*, *Juniperus chinensis*, and *Dioscorea bulbifera* [8].

In styryl chromones, 4*H*-1-benzopyran-4-ones with styryl (phenylethenyl) substituent at 2-position has a distinct place in the realm of flavonoid chemistry. Hormothamnione, the first naturally occurring example of 2-styrylchromone was isolated from blue-green algae *Hormothamnion enteromorphoides* which have shown potent invitro cytotoxicity against human leukemia cells [9]. Synthetic derivatives of 2-styrylchromones have also been reported to show promising antitumor and anti-allergic activities [10,11]. It has been demonstrated that certain synthetic derivatives are inhibitors of the replication of both 1B and 14 serotypes of the human anti-rhinovirus [12], and 3′-allyl-5,7,4′-trimethoxy-2-styrylchromone uncouples oxidative phosphorylation [13] and some other act as potent xanthine oxidase inhibitors [14], antiproliferative agents targeting carcinoma cells [15], β-amyloid imaging agents [16] and shows anti-inflammatory potential [17].

2-Styrylchromones, because of their conjugated diene structure, in which one of the double bonds is part of the heterocyclic ring, undergo Diels-Alder reaction with different dienophiles to afford the condensed heterocyclic system, which otherwise are difficult to prepare [18,19].

Although, 2-styrylchromones ((*E*)-2-styryl-4*H*-chromen-4-ones) are seldom in nature but have been synthesized largely, and various strategies have been adopted for their synthesis which include: Allan-Robinson condensation [20], Baker-Venkataraman rearrangement [21], cyclization of an acetylenic ketone [22], intramolecular Wittig reaction

[23], condensation of 2-methylchromones with benzaldehydes [24] and aldol condensation followed by oxidative cyclization [25].

Further, the introduction of a hydroxyl group at C-3 position to 2-styrylchromones (give 3-hydroxy-2-styrylchromones) improves the antirhinovirus activity against both A and B serotypes of human rhinovirus [26]. Also, no reports of naturally occurring 3-hydroxy-2-styrylchromones are available in the literature so far. Keeping in view the significant biological properties and scarcity of these 2-styrylchromones [4], the synthesis of 3-hydroxy-2-styrylchromones has been considered. Few reports are available for the synthesis of 3-hydroxy-2-styrylchromones via the Algar-Flynn-Oyamada reaction using hydrogen peroxide in the alkaline medium using H_2O_2-NaOH/EtOH, H_2O_2-KOH/MeOH, H_2O_2-NaOH/THF-MeOH, H_2O_2-NEt_2/DMSO:1,4-Dioxane as oxidizing agents [27–34].

But the above-mentioned conditions suffer from one or the other limitations, as hydrogen peroxide is available only as an aqueous solution (30–40 %) and its use increases the amount of water in the reaction mixture, as a result of which makes 1-(2′-hydroxyphenyl)-5-aryl-penta-2,4-dien-1-ones insoluble. Further addition of a sufficient amount of pyridine is required to homogenize the reaction mixture as a result of which a bulk of the reaction mixture increases [35]. Also, as the reaction is being carried out under heating conditions, the formation of 2-cinnamylidene-3(2H)-benzofuranones may also be accompanied during the reaction, making the purification of the required 3-hydroxy-2-styrylchromones difficult and these are obtained in very low yields.

These shortcomings led us to develop a rapid, safe, and environmentally benign method for the synthesis of 3-hydroxy-2-styrylchromones using UHP (urea-hydrogen peroxide), avoiding the use of pyridine, a highly toxic substance using grinding technique.

In the last few years, the grinding technique has increasingly been used in organic synthesis. It has got much attention due to its operational simplicity and is also recognized as an important tool to carry out the reactions under solvent-free conditions with minimum cost and maximum yield as compared to conventional methods [36,37]. Moreover, this technique is also used on an industrial scale, by using an electric food mixer with stainless steel rotors, or by using a ball mill [38]. So, in continuation of our work on the synthesis of organic compounds using the grinding technique [39], here we have developed an efficient method for the synthesis of 3-hydroxy-2-styrylchromones using UHP (urea-hydrogen peroxide) under solvent-free conditions using the grinding technique (Scheme 1).

Scheme 1. Synthesis of 3-hydroxy-2-styrylchromones using grinding technique.

2. Results and Discussion

Herein, we wish to report a facile and efficient protocol for the synthesis of 3-hydroxy-2-styrylchromones (Scheme 1) making use of UHP [40] as a source of hydrogen peroxide, which avoids the bulk of the reaction mixture and thus the reaction carried out avoiding pyridine, a toxic reagent under grinding conditions. A mixture of 1-(2′-hydroxyphenyl)-5-aryl-penta-2,4-dien-1-ones, UHP, and potassium hydroxide moist with a few drops of ethanol, on grinding with a mortar in a pestle at room temperature, afforded 3-hydroxy-2-styrylchromones in excellent yield in one step (Scheme 1). The compound was extracted after acidification of the reaction mixture in cold concentrated HCl. As the reaction is being carried out at room temperature, it suppresses the formation of 2-

cinnamylidene-3(2*H*)-benzofuranones as side products, generally formed at elevated temperatures; this is confirmed by using thin layer chromatography, thus resulting in 3-hydroxy-2-styrylchromones in higher yields. An IR spectrum of the product formed showed an absorption at 3250 cm^{-1} due to O-H stretching and absorption at 1610 cm^{-1} due to C=O stretching. A ^{1}H-NMR spectrum showed a singlet at δ 9.60, a doublet at δ 8.05, and a multiplet at δ 7.85–7.55, due to OH, -CH=CH-, and aromatic protons, respectively. Further, the formation of 3-hydroxy-2-styrylchromones was confirmed by comparing the melting point with the literature value [33,35] (Table 1).

The present method is simple, as UHP has been used as a source of hydrogen peroxide, which avoids the bulk volume of the reaction and makes handling easy. Moreover, the present method avoids the use of hazardous and toxic solvents, making the reaction eco-friendly.

Table 1. Physical data of 3-hydroxy-2-styrylchromones synthesised via modified AFO reaction.

Compound	R	R′	Time (min) (a + b)	Yield [c] (%)	Mp [d] (°C)
2a	H	H	5 + 5	92	188–190
2b	H	4′-OCH_3	5 + 5	92	217–220
2c	H	4′-Cl	5 + 5	90	220–222
2d	H	4′-NO_2	5 + 10	88	222–225
2e	6-Cl	H	5 + 10	90	220–222
2f	6-Cl	4′-OCH_3	5 + 10	85	218–222
2g	6-Cl	4′-Cl	5 + 10	88	220–222
2h	6-Cl	4′-NO_2	5 + 5	90	222–225
2i	6-F	H	5 + 10	90	225–228
2j	6-CH_3	H	5 + 10	88	229–230
2k	5,7-CH_3	H	5 + 10	85	194–196

a: grinding time; b: time for digestion; [c]: Isolated yields. [d]: melting points are uncorrected and compared with literature values [26,33].

3. Experimental Section

Melting points were determined in open capillaries. The IR spectra were recorded on a Perkin-Elmer spectrum BX series FT-IR spectrophotometer with KBr pellets. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Avance (400 MHz & 100 MHz) instruments respectively using TMS as the internal standard. All the chemicals were obtained commercially and used without further purification. 1-(2′-Hydroxy-phenyl)-5-aryl-penta-2,4-dien-1-ones required for the present study were prepared using the method available in the literature [26].

General Procedure for the Synthesis of 3-Hydroxy-2-styrylchromones **2a–2k**

A mixture of 1-(2′-Hydroxy-phenyl)-5-aryl-penta-2,4-dien-1-ones (1 mmol), urea-hydrogen peroxide complex (UHP) (2 mmol), and pulverized potassium hydroxide homogenized with 5–10 drops of ethanol (approx. 0.1–0.2 mL) was ground with a mortar in a pestle at room temperature for 5.0 min. The completion of the reaction was monitored by thin layer chromatography, confirming the presence of a single product. The reaction mixture was left at room temperature for another 10 min for digestion which was further diluted with ice-cold water, and acidified with concentrated HCl. The solid thus obtained was filtered, washed with water, and recrystallized from ethanol to give 3-hydroxy-2-styrylchromones.

4. Conclusions

The present approach for the synthesis of 3-hydroxy-2-styrylchromones using UHP via the Algar-Flynn-Oyamada reaction is highly efficient and eco-friendly as it avoids the use of organic solvents at any stage of the reaction. This is a clean, mild, highly yielded, and expeditious method avoids the formation of any 2-cinnamylidene-3(2*H*)-benzofuranones by-products.

Funding: This research received no external funding from any agency.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement:

Acknowledgments: The author is very much grateful to Late. J.K Makrandi, (Retd.), Department of Chemistry, Maharishi Dayanand University, Rohtak, India for his endless support to carried out this research work.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Sugita, Y.; Takao, K.; Uesava, Y.; Nagai, J.; Lijima, Y.; Sano, M.; Sakagami, H. Development of newly synthesized chromone derivatives with high tumor specificity against human oral squamous cell carcinoma. *Medicines* **2020**, *7*, 50.
2. Takao, K.; Endo, S.; Nagai, J.; Kamauchi, H.; Takemura, Y.; Uesawa, Y.; Sugita, Y. 2-Styrylchromone derivatives as potent and selective monoamine oxidase B inhibitors. *Bioorg. Chem.* **2019**, *92*, 103285.
3. Uesawa, Y.; Nagai, J.; Shi, H.; Sakagami, H.; Bandow, K.; Tomomura, A.; Tomomura, M.; Endo, S.; Takao, K.; Sugita, Y. Quantitative structure–cytotoxicity relationship of 2-styrylchromones. *Anticancer Res*. **2019**, *39*, 6489–6498.
4. Gomes, A.; Freitas, M.; Fernandes, E.; Lima, J.L.F.C. Biological activities of 2-styrylchromones. *Mini Rev. Med. Chem.* **2010**, *10*, 1–7.
5. Keri, R.S.; Budagumpi, S.; Pai, R.K.; Balakrishna, R.G. Chromones as a privileged scaffold in drug discovery: A review. *Eur. J. Med. Chem.* **2014**, *78*, 340–374.
6. Gaspar, A.; Matos, M.J.; Garrido, J.; Uriarte, E.; Borges, F. Chromone: A valid scaffold in medicinal chemistry. *Chem. Rev*. **2014**, *114*, 4960–4992.
7. Sharma, K.S.; Kumar, S.; Chand, K.; Kathuria, A.; Gupta, A.; Jain, R. An update on natural occurrence and biological activity of chromones. *Curr. Med. Chem.* **2011**, *18*, 3825–3852.
8. Santos, C.M.M.; Silva, A.M.S. An overview of 2-styrylchromones: Natural occurrence, synthesis, reactivity and biological properties. *Eur. J. Org. Chem.* **2017**, *2017*, 3115–3133.
9. Gerwick, W.H.; Lopez, A.; Van Duyne, G.D.; Clardy, J.; Ortiz, W.; Baez, A. Hormothamnione, a novel cytotoxic styrylchromone from the marine cyanophyte hormothamnion enteromorphoides grunow. *Tetrahedron Lett.* **1986**, *27*, 1979–1982.
10. Doria, G.; Romeo, C.; Forgione, A.; Saberze, P.; Tibolla, N.; Corno, M.L.; Cruzzola, G.; Cadelli, G. Synthesis and antiallergic activity of 2-styrylchromones. *Eur. J. Med. Chem. Chim. Ther.* **1979**, *14*, 347–351.
11. Brion, J.D.; Le Baut, G.; Zammattio, F.; Pierre, A.; Atassi, G.; Belachmi, L. New Heterocyclic Compounds: 2-Styryl-4h-1-Benzopyran-4-ones process for their preparation and pharmaceutical compositions containing them. *Eur. Pat. Appl. EP* 454 **1991**, 587. *Chem. Abstr.* **1992**, *116*, 106092k.
12. Desideri, N.; Conti, C.; Mastromarino, P.; Mastropaolo, F. Synthesis and Anti-Rhinovirus Activity of 2-Styrylchromones. *Antivir. Chem. Chemother.* **2000**, *11*, 373–381.
13. Peixoto, F.; Barros, A.I.R.N.A.; Silva, A.M.S. Interactions of a new 2-styrylchromone with mitochondrial oxidative phosphorylation. *J. Biochem. Mol. Toxicol.* **2002**, *16*, 220–226.
14. Fernandes, E.; Carvalho, F.; Silva, A.M.S.; Santos, C.M.M.; Pinto, D.C.G.A.; Cavaleiro, J.A.S.; Bastos, M. de L. 2-Styrylchromones As Novel Inhibitors of Xanthine Oxidase. A Structure-activity Study. *J. Enzym. Inhib. Med. Chem.* **2002**, *17*, 45–48.
15. Shaw, A.Y.; Chang, C.-Y.; Liau, H.-H.; Lu, P.-J.; Chen, H.-L.; Yang, C.-N.; Li, H.-Y. Synthesis of 2-styrylchromones as a novel class of antiproliferative agents targeting carcinoma cells. *Eur. J. Med. Chem.* **2009**, *44*, 2552–2562.
16. Ono, M.; Maya, Y.; Haratake, M.; Nakayama, M. Synthesis and characterization of styrylchromone derivatives as β-amyloid imaging agents. *Bioorganic Med. Chem.* **2007**, *15*, 444–450.
17. Gomes, A.; Fernandes, E.; Silva, A.M.S.; Pinto, D.C.G.A.; Santos, C.M.M.; Cavaleiro, J.A.S.; Lima, J.L.F.C. Anti-inflammatory potential of 2-styrylchromones regarding their interference with arachidonic acid metabolic pathways. *Biochem. Pharmacol*. **2009**, *78*, 171–177.
18. Schonberg, A.; Mustafa, A.; Aziz, G. Diels-Alder Reaction. II. Experiments with 2-Styrylchromones. On the Nature of the Dimer of 1,3-Diphenylisobenzofuran. *J. Am. Chem. Soc.* **1954**, *76*, 4576–4577.
19. Mustafa, A.; Ali, M.I. 2-Styrylchromones in the Diene Synthesis. *J. Org. Chem.* **1956**, *21*, 849–851.

20. Robinson, R.; Shinoda, J. CCLXV.-The synthesis of certain 2-styrylchromonol derivatives. *J. Chem. Soc. Trans.* **1925**, *127*, 1973–1980.
21. Baker, W. 322. Molecular rearrangement of some o-acyloxyacetophenones and the mechanism of the production of 3-acylchromones. *J. Chem. Soc.* **1933**, 1381–1389. https://doi.org/10.1039/JR9330001381.
22. Obrecht, D. Acid-Catalyzed Cyclization Reactions of Substituted Acetylenic Ketones: A new Approach for the Synthesis of 3-Halofurans, Flavones, and Styrylchromones. *HCA* **1989**, *72*, 447–456.
23. Zammattio, F.; Brion, J.D.; Ducrey, P.; Le Baut, G. New route to styrylchromones via [1-(2-hydroxybenzoyl) alkylidene] triphenylphosphoranes. *Synthesis* **1992**, *4*, 375–376.
24. Helibron, I.M.; Barnes, H.; Morton, R.A. CCXCIV.-Chemical reactivity and conjugation: The reactivity of the 2-methyl group in 2:3-dimethylchromone. *J. Chem. Soc., Trans.* **1923**, *123*, 2559–2570.
25. Cheema, U.S.; Gulati, K.C.; Venkataraman, K. Synthetical experiments in the chromone group. Part VI. 2-Styrylchromones. *J. Chem. Soc.* **1932**, 925–933. https://doi.org/10.1039/JR9320000925.
26. Desideri, N.; Mastromarino, P.; Conti, C. Synthesis and evaluation of antirhinovirus activity of 3-hydroxy and 3-methoxy 2-styrylchromones. *Antivir. Chem. Chemother.* **2003**, *14*, 195–203.
27. Gupta, S.C.; Yusuf, M.; Sharma, S.; Saini, A.; Arora, S.; Kamboj, R.C. Phototransformations of some 3-alkoxy-2-styrylchromones: Type II cyclisations of 1,4- and 1,6-biradicals. *Tetrahedron* **2004**, *60*, 8445–8454.
28. Jain, N.; Gambhir, G.; Krishnamurty, H.G. Synthesis of hormothamnione and 6-desmethoxyhormothamnione. *Indian J. Chem.* **2001**, *40*, 278–283.
29. Conti, C.; Mastromarino, P.; Goldoni, P.; Portalone, G.; Desideri, N. Synthesis and Anti-Rhinovirus Properties of Fluoro-Substituted Flavonoids. *Antivir. Chem. Chemother.* **2005**, *16*, 267–276.
30. Marini-Bettòlo, G.B. Synthesis of flavonoids. *Gazzeta* **1942**, *72*, 201–205.
31. Dean, F.M.; Podimuang, V. The course of the Algar–Flynn–Oyamada (A.F.O.) reaction. *J. Chem. Soc.* **1965**, 3978–3987. https://doi.org/10.1039/JR9650003978.
32. Dhoubhadel, S.P.; Tuladhar, S.M.; Tuladhar, S.M.; Wagley, P.P. Synthesis of some 3-methoxyflavones and chromones. *Indian J. Chem. Sect. B-Org. Chem. Incl. Med. Chem.* **1981**, *20*, 511–512.
33. Bennett, M.; Burke, A.J.; O'Sullivan, W.I. Aspects of the Algar-Flynn-Oyamada (AFO) reaction. *Tetrahedron* **1996**, *52*, 7163–7178.
34. Bhattacharyya, S.; Hatua, K. Computational insight of the mechanism of Algar–Flynn–Oyamada (AFO) reaction. *RSC Adv.* **2014**, *4*, 18702–18709.
35. Seshadri, S.; Trivedi, P. Reactions of Nitrohydroxychalcones. Oxidation by Hydrogen Peroxide in Alkaline Medium. *J. Org. Chem.* **1960**, *25*, 841–843.
36. Kumar, D.; Kumar, S.; Makrandi, J.K. Aqueous-mediated green synthesis of 3-carboxyxoumarins using grinding technique. *Green Chem. Lett. Rev.* **2015**, *8*, 21–25.
37. Sharma, D.K.; Kumar, S. A facile synthesis of 3-chloro-2-phenyl-4H-chromen-4-ones using grinding technique at room temperature. *Bulg. Chem. Commun.* **2017**, *49*, 309–312.
38. Bose, A.K.; Pednekar, S.; Ganguly, S.N.; Chakraborty, G.; Manhas, M.S. A simplified green chemistry approach to the Biginelli reaction using 'Grindstone Chemistry'. *Tetrahedron Lett.* **2004**, *45*, 8351–8353.
39. Sharma, D. An efficient and eco-friendly synthesis of quinolinyl chalcones under solvent-free conditions at room temperature. *Res. Chem. Intermed.* **2015**, *41*, 927–933.
40. Lu, C.S.; Hughes, E.W.; Giguère, P.A. The Crystal Structure of the Urea-Hydrogen Peroxide Addition Compound $CO(NH_2)_2 \cdot H_2O_2$. *J. Am. Chem. Soc.* **1941**, *63*, 1507–1513.