chemistry proceedings

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Organocatalytic Synthesis of 2H-Flavenes and Evaluation of Their Reactivity in Michael Versus Knoevenagel Reactions †

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† Presented at the 29th International Electronic Conference on Synthetic Organic Chemistry (ECSOC-29); Available online: https://sciforum.net/event/ecsoc-29.

Abstract

In this work we report the stereoselective synthesis of 2H-flavenes via an aminocatalytic privileged Diversity-Oriented Synthesis (ApDOS) strategy. An oxa-Michael cyclization between salicylaldehydes and an iminium intermediate from cinnamaldehyde and the Hayashi–Jørgensen catalyst afforded flavenes in up to 81% yield and 90% ee under optimal conditions (PhCOOH, toluene, 40 °C, 18 h). In general, the reaction proceeds with good yields. Further, reaction with a stabilized carbanion produced Knoevenagel-type adducts, explained by electronic delocalization, HSAB considerations, and kinetic/thermodynamic factors. The resulting polycyclic products show potential as dienophiles in Diels–Alder reactions, offering valuable scaffolds for future bioactive compound development.

Keywords: iminium ion activation; 2H-flavenes; oxa-Michael; knoevenagel

1. Introduction

The stereocontrolled synthesis of privileged structures based on natural architectures, constitute an important topic in the contemporary organic chemistry, The ability of such compound to exert significant biological activity have allowed the development of a wide variety of synthetic methodologies [1]. Traditionally, the synthesis of bioactive compounds has been through concept of Target-Oriented Synthesis (TOS), which emphasizes assembling a compound by a retrosynthetic analysis. In contrast, Diversity-Oriented Synthesis (DOS) allows the creation of structurally diverse libraries from common substrates [2].

For years, the aminocatalysis has remained as an important tool in the field of organocatalysis, its relevance lies in the ability to develop a broad range of methodologies through the different catalytic pathways. In this sense, Aminocatalytic privileged Diversity-Oriented Synthesis (ApDOS), has emerged as a versatile strategy, which expands structural diversity through various activation modes under stereochemical control [3].

In terms of privileged frameworks, flavonoids are a large family of secondary metabolites characterized by a C6–C3–C6 structural motif with various pharmacological effects, including antioxidant, antiviral, and anti-inflammatory activities. Particularly, the 2H-flavenes are notable for their structural properties and biological potential, which

Academic Editor(s): Name

Published: date

Citation: Mares, X.N.A.; Cruz, D.C.; Gómez, C.V. Organocatalytic Synthesis of 2H-Flavenes and Evaluation of Their Reactivity in Michael Versus Knoevenagel Reactions. *Chem. Proc.* **2025**, *volume number*, x. https://doi.org/10.3390/xxxxx

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range from the cytotoxic natural product candenatenin E to synthetic derivatives such as acolbifene, a selective estrogen receptor modulator [4].

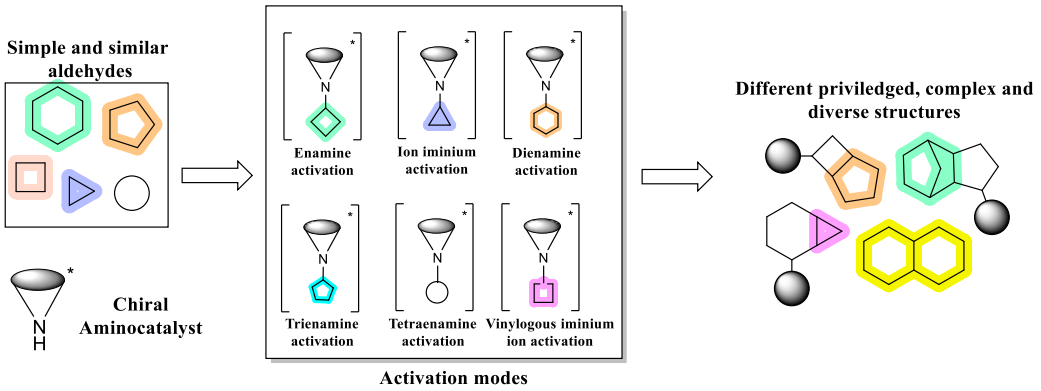


Figure 1. ApDOS concept.

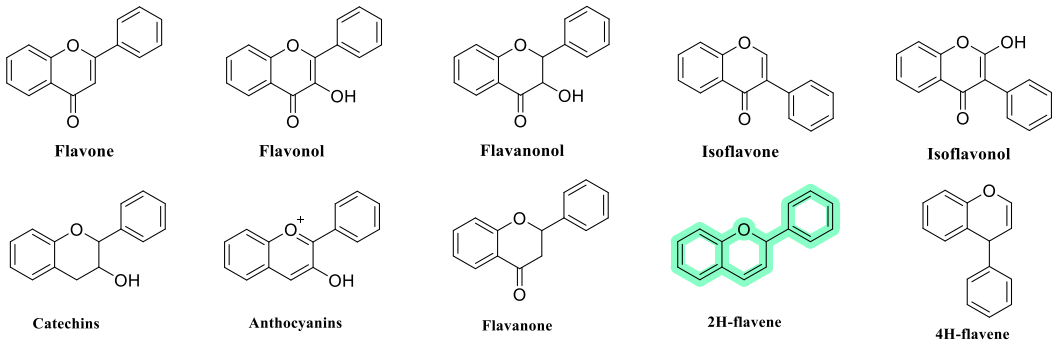


Figure 2. Classification and structural variants of flavonoid.

Considering the important properties of the 2H-flavenes, several methodologies have been stablished for their synthesis, including the asymmetric synthesis via aminocatalysis. In 2006, Arvidsson reported the first oxa-Michael route using the Hayashi–Jørgensen catalyst. Later, in 2007, Córdova and Wang improved the selectivity and yields by both, the optimization of the conditions and the use of a different organocatalyst [5–7].

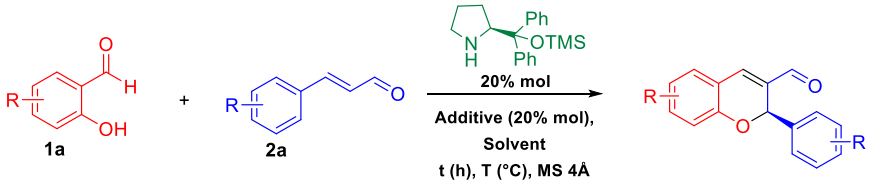
2. Methodology

All starting materials and reagents employed in this study were commercially sourced unless otherwise specified. Proton ^{1}H NMR spectra were obtained using a Bruker 400 MHz spectrometer. Flash column chromatography was performed on silica gel using mixtures of hexane/ethyl ether, as well as hexane/ethyl acetate, as eluents.

3. Results and Discussions

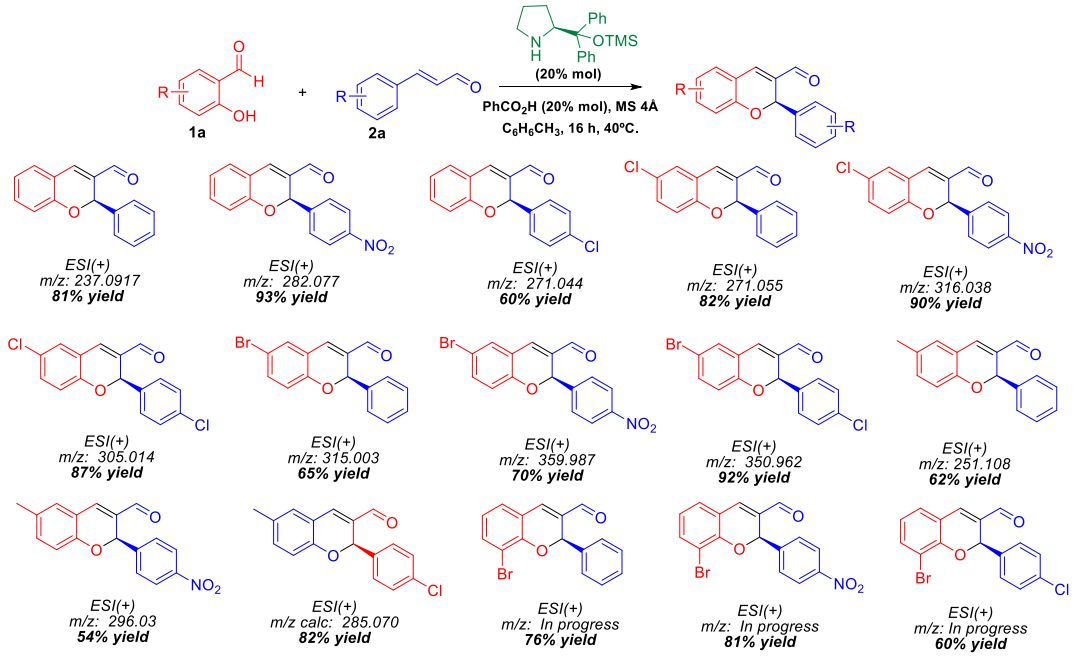
Initially, the conditions reported by Córdova and co-workers for the flavene synthesis were reproduced. However, an optimization was necessary because the initial results were not fully satisfactory.

Table 1. Optimization of the aminocatalytic oxa-Michael reaction for the synthesis of 2H-flavenes.



Entry	Solvent	T (°C)	Additive	Equiv. 1a	Equiv. 2a	t (h)	Yield (%)	% ee
1	Toluene	25	$PhCO_2H$	1.2	1.0	72	68	In progress
2	Toluene	25	p-NO_2-$PhCO_2H$	1.2	1.0	72	60	In progress
3	Toluene	40	p-NO_2-$PhCO_2H$	1.2	1.0	16	76	In progress
4	Toluene	40	$PhCO_2H$	1.2	1.0	16	81	90
5	Toluene	40	$PhCO_2H$	1.0	1.2	16	51	60
6	Dioxane	40	$PhCO_2H$	1.2	1.0	18	56	In progress
7	Dioxane	70	$PhCO_2H$	1.2	1.0	16	46	In progress
8	Chloroform	40	$PhCO_2H$	1.2	1.0	48	44	In progress
9	Acetonitrile	40	$PhCO_2H$	1.2	1.0	48	56	In progress

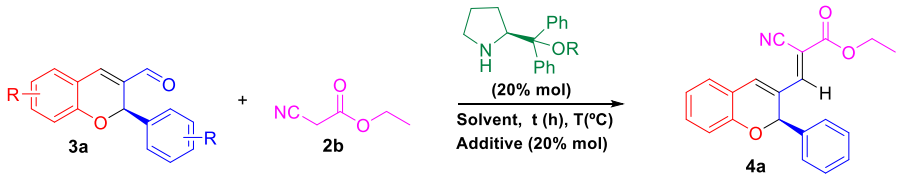
Once the reaction conditions were optimized (entry 4), the scope and limitations of the reaction were explored by synthesizing derivatives with different substitution patterns on salicylaldehyde and cinnamaldehyde. In this sense, whole the products were efficiently obtained through the iminium-ion activation mode, confirming the versatility of the proposed strategy (Scheme 1).



Scheme 1. Scope and limitations for the synthesis of flavenes.

With the 2H-flavenes in hand, we explored an organocatalytic post-functionalization through the Michael addition of a stabilized carbanion to the iminium ion formed by condensation of the aldehyde from the flavene with an aminocatalyst. However, an unexpected Knoevenagel reaction resulted when the enolate from **2b** was used (Table 2). This transformation occurred in high yields and was reproducible under different solvents and temperatures.

Table 2. Knoevenagel functionalization of 2H-flavenes with a stabilized carbanion under different conditions.



Entry	Solvent	Temp (°C)	Equiv. 3a	Equiv. 2b	Time (h)	Yield (%)
1	Chloroform	25	1.0	2.0	24	95
2	Toluene	25	1.0	2.0	24	93
3	Toluene	40	1.0	2.0	24	86

This behavior can be explained by considering the electronic delocalization of the 2*H*-flavene system, as well as Pearson's Hard–Soft Acid–Base (HSAB) principles and both kinetic and thermodynamic factors, which favor the condensation over addition. The formation of the Knoevenagel-type product was confirmed by ^{1}H NMR, high-resolution mass spectrometry (HRMS), and X-ray diffraction.

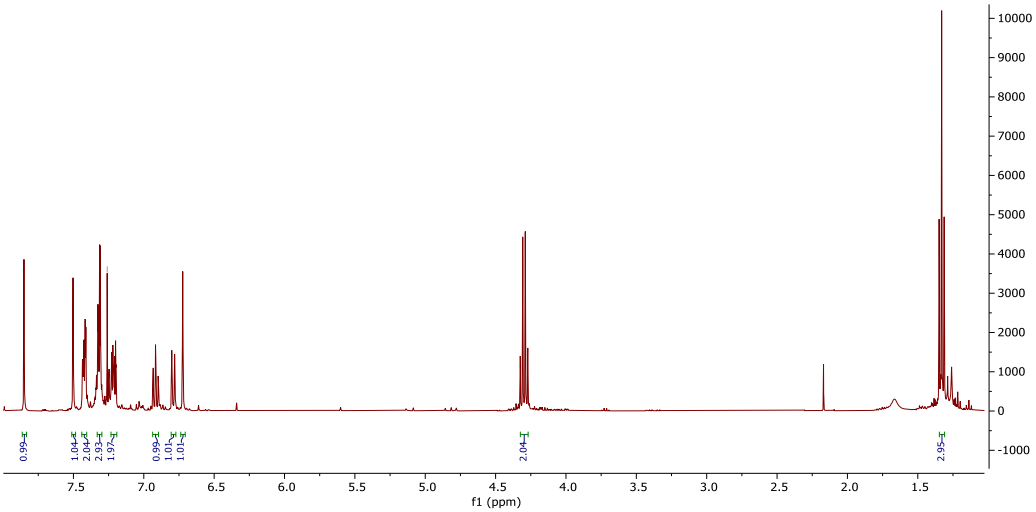


Figure 3. Representative ^{1}H-NMR signals of the Knoevenagel product.

4. Conclusions

An efficient stereoselective methodology for the synthesis of 2*H*-flavenes was developed through organocatalysis using an iminium-ion activation (up to 81% yield, 90% ee). The strategy is versatile for different salicylaldehydes and cinnamaldehydes. Additionally, a post-fuctionalization with a stabilized carbanion afforded to Knoevenagel-type products rather than Michael adducts, which can be rationalized by electronic delocalization of the flavene system and according to the HSAB theory. Overall, this work demonstrates that the ApDOS strategy provides not only enantioselective access to bio-inspired flavenes but also new structural diversifications, opening opportunities for the synthesis of bioactive molecules and future new transformations.

Author Contributions: Conceptualization, D.C.C. and C.V.G.; methodology, X.N.A.M.; validation, D.C.C. and C.V.G.; formal analysis, X.N.A.M.; investigation, X.N.A.M.; resources, D.C.C. and C.V.G.; data curation, X.N.A.M.; writing—original draft preparation, X.N.A.M.; writing—review and editing, D.C.C. and C.V.G.; supervision, D.C.C. and C.V.G.; project administration, D.C.C. and C.V.G.; funding acquisition, D.C.C. and C.V.G. All authors have read and agreed to the published version of the manuscript.

Funding:

Institutional Review Board Statement:

Informed Consent Statement:

Data Availability Statement:

Acknowledgments: This work was made possible thanks to the support provided by SECIHTI, Proyecto de Ciencia Básica y de Frontera 2023-2024 (project code: CBF2023-2024-266), Becas Nacionales para estudios de Posgrado 2024-2 call (scholarship No. 4024012), and the Laboratorio Nacional de Caracterización de Propiedades Fisicoquímicas y Estructura Molecular (LANCAPFEM) UG.

Conflicts of Interest:

References

1. Welsch, M.E.; Snyder, S.A.; Stockwell, B.R. Privileged scaffolds for library design and drug discovery. *Chem. Biol.* **2010**, *14*, 347–361.
2. Shereiber, S.L. Target-oriented and diversed-oriented organic synthesis drug discovery. *Science* **2000**, *284*, 1964–1969.
3. Jiang, H.; Albrecht, L.; Jørgensen, K.A. Aminocatalytic remote functionalization strategies. *Chem. Sci.* **2013**, *4*, 2287.
4. Govender, T.; Hojabri, L.; Moghaddam, F.M.; Arvidsson, P.I. Organocatalytic synthesis of chiral benzopyrans. *Tetrahedron Asymmetry* **2006**, *17*, 1763.
5. Sundén, H.; Ibrahem, I.; Zhao, G.-L.; Eriksson, L.; Córdova, A. Catalytic enantioselective domino oxa Michael/Aldol condensations: Asymmetric synthesis of benzopyran derivatives. *Chem. Eur. J.* **2007**, *13*, 574.
6. Li, H.; Wang, J.; E-Nunu, T.; Zu, L.; Jiang, W.; Wei, S.; Wang, W. One-pot approach to chiral chromenes via enantioselective organocatalytic domino oxa-Michael-aldol reaction. *Chem. Commun.* **2007**, *2007*, 507.

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