chemistry proceedings

Proceeding Paper

Study on Diels–Alder Reaction of Spilanthol †

Rodrigo Barrón Velázquez, Mariana Macías Alonso, Edgar Juárez Robles and Joaquín González Marrero *

Instituto Politécnico Nacional—UPIIG, Av. Mineral de Valencia No. 200, Col. Fracc. Industrial Puerto Interior, Silao de la Victoria 36275, Guanajuato, Mexico; email1@email.com (R.B.V.); email2@email.com (M.M.A.); email3@email.com (E.J.R.)

* Correspondence: jgonzalezm@ipn.mx

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

Abstract

This study explores the Diels–Alder reaction using spilanthol, a natural diene isolated from *Heliopsis longipes* roots, to synthesize potentially bioactive compounds. Spilanthol was purified through silica gel column chromatography, yielding 16 g/kg of dried roots, and characterized by ^{1}H NMR spectroscopy. Among the dienophiles tested, only *p*-anisaldehyde reacted efficiently in the presence of $BF_3{\cdot}OEt_2$ as a Lewis acid catalyst. A cyclic adduct was obtained with yields of 9.72% (endo) and 24.32% (exo). ^{1}H NMR analysis confirmed the formation of a pyran ring, demonstrating the viability of this synthetic pathway for producing functionalized cyclic compounds with potential biological activity.

Keywords: Diels-Alder; spilanthol; bioeconomy

Academic Editor(s): Name

Published: date

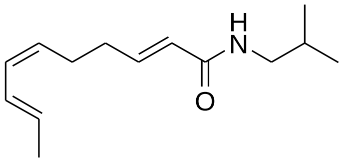
Citation: Velázquez, R.B.; Alonso, M.M.; Robles, E.J.; Marrero, J.G. Study on Diels–Alder Reaction of Spilanthol. *Chem. Proc.* **2025**, *volume number*, x. https://doi.org/10.3390/xxxxx

Copyright: © 2025 by the authors. Submitted for possible open access publication under the terms and conditions of the Creative Commons Attribution (CC BY) license (https://creativecommons.org/licenses/by/4.0/).

1. Introduction

Spilanthol **1** (Scheme 1), *N*-isobutyl-(2E,6Z,8E)-deca-2,6,8-trienamide, is an alkylamide isolated from the roots of Heliopsis longipes, a medicinal plant endemic to regions of Mexico such as the Sierra Álvarez and Sierra Gorda [1]. Its architecture—an unsaturated amide appended to a conjugated diene—renders spilanthol **1** a competent diene for Diels–Alder cycloadditions [2]. Beyond its synthetic utility, spilanthol **1** displays analgesic, anti-inflammatory, antimicrobial, and antioxidant activities, underscoring its pharmacological promise [3]. Leveraging these features, spilanthol **1** can serve as a renewable scaffold for the sustainable construction of bioactive heterocycles.

In this study, we assess the feasibility and selectivity of the Diels–Alder reaction between spilanthol **1** and *p*-anisaldehyde. We further examine the influence of different catalysts on yield and selectivity, aiming to optimize conditions and advance greener, more efficient synthetic methodologies.



Spilanthol **1**

Scheme 1. Chemical structure of spilanthol **1** (2E,6Z,8E)-N-isobutyl-2,6,8-decatrienamide.

2. Materials and Methods

2.1. Extraction and Identification of Spilanthol 1

Ten grams of ground root og *H. longipes* were macerated in absolute ethanol (1:10 *w*/*v*) for one week, repeated three times with fresh solvent. The extract was filtered, evaporated, and analysed via thin-layer chromatography using hexane/ethyl acetate (3:2), identifying the target compound with an Rf = 0.3. Structural identification was confirmed by proton nuclear magnetic resonance spectroscopy (^{1}H-NMR, 400 MHz, $CDCl_3$), comparing chemical shifts with reported literature data [4].

Spilanthol ***1***. IR (film) ν_{max}: 3276, 2958, 2928, 2871, 1669, 1629, 1552, 1247, 1159, 980, 947, 820 cm^{-1}.^{1}HNMR ($CDCl_3$, 400 MHz) δ_H: 6.85 (dt, 1H, J_1 15.0 Hz, J_2 6.6 Hz, H-3), 6.30–6.26 (m, 1H, H-8), 5.97 (dd, 1H, $J_1 = J_2$ = 10.8 Hz, H-7), 5.80 (dt, 1H, J_1 15.6 Hz, J_2 1.8 Hz, H-2), 5.70 (dq, 1H, J_1 12.0, J_2 6.0, H-9), 5.52 (br, s, 1H, NH), 5.26 (dt, 1H, J_1 10.8 Hz, J_2 7.2 Hz, H-6), 3.15 (dd, 2H, $J_1 = J_2$ 6.3 Hz, H-1′), 2.36–2.22 (m, 4H, H-4 and H-5), 1.82–1.77 (m, 2H, H-2′ and H-10), 0.92 (d, 1H, J 6.0 Hz, H-3′ and H-4′) ppm; ^{13}CNMR ($CDCl_3$, 100 MHz) δ_C: 165.9 (C=O), 143.4 (C-3), 129.9 (C-9), 129.4 (C-7), 127.8 (C-6), 126.6 (C-8), 124.1 (C-2), 46.8 (C-1′), 32.1 (C-4), 28.6 (C-2′), 26.4 (C-5), 20.1 (C-3′ andC-4′), 18.3 (C-10) ppm; EIMS *m*/*z* (%) 221 (M$^+$, 6), 141 (61), 126 (17), 98 (18), 81 (100), 79 (19), 41 (31); HREIMS *m*/*z* 221.1801 (calcd for $C_{14}H_{23}NO$ 221.1779).

2.2. Diels-Alder Reaction

A solution of spilanthol 1 (1 mmol), the corresponding dienophile (1 mmol), and 5 mol% of catalyst in dry tetrahydrofuran (THF, 0.2 M) was stirred for 24 h under two conditions—at room temperature and under reflux —while monitoring progress by TLC and visualized with potassium permanganate; upon completion, distilled water was added, and the mixture was extracted with dichloromethane (3 × 25 mL), after which the combined organic layers were dried, filtered, and concentrated under reduced pressure, and the crude product was purified by silica gel column chromatography using a hexane/ethyl acetate gradient (100:0 to 80:20), affording a purified adduct that was analyzed by ^{1}H-NMR to determine chemical structure.

Compound **2**: ^{1}H NMR (400 MHz, $CDCl_3$) δ ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (m), 6.80 (m), 5.90 (d), 5.75 (m), 5.58 (Br s), 5.35 (m), 4.20 (m), 2.40 (m, 1H), 1.95 (m, 2H), 1.90 (s, 3H), 1.01 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 145.9, 138.6, 132.9, 129.0, 128.9, 128.4, 128.2, 126.1, 124.1, 122.4, 82.9, 77.0, 47.1, 36.4, 35.7, 28.7, 26.9, 20.4, 20.3, 15.2; EIMS *m*/*z* (%) *327* (M$^+$, *16*), *328* (*23*), *133* (17), 98 (18), 81 (100); HREIMS *m*/*z* *327*.2215 (calcd for $C_{21}H_{29}NO_2$ *327*.2201).

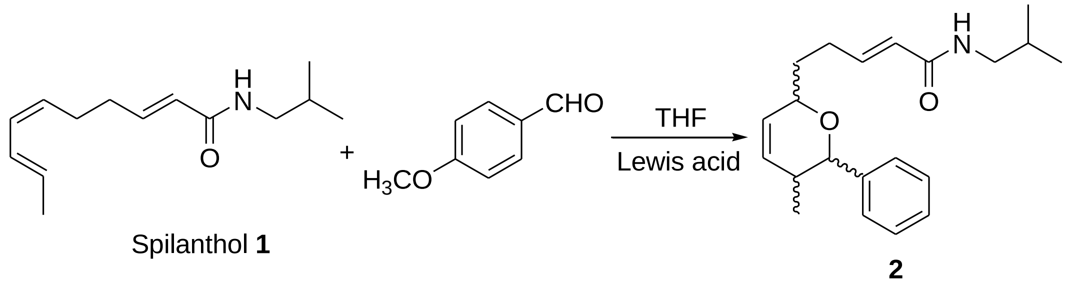
3. Results and Discussion

3.1. Isolation and Characterisation of Spilanthol 1

The isolated compound, purified from the ethanolic extract of *Heliopsis longipes*, was then subjected to ^{1}H NMR analysis. The spectrum exhibited characteristic chemical shift signals corresponding to specific proton environments. Three methyl group signals (–CH_3) were observed at δ_H 0.93 and 1.74 ppm, along with a methine proton (–CH–) at δ_H 1.76 ppm. Three methylene group signals (–CH_2–) were detected in the δ_H 2.35–2.40 ppm region. Additionally, five olefinic protons (C=CH) were identified in the δ_H 5.59–6.00 ppm range. The proton signals were consistent with those previously reported in the literature [5], supporting the structural identification of the compound. The extraction yielded approximately 16 g of Spilanthol **1** per kilogram of dried root material.

3.2. Diels-Alder Reaction Between Spilanthol 1 and p-Anisaldehyde

The Diels-Alder reaction between spilanthol **1** and *p*-anisaldehyde was examined to probe diene–dienophile reactivity under thermal conditions and in the presence of Lewis acids (Scheme 2). Reactions were first run without a catalyst in dry THF, exploring two temperature regimes to distinguish kinetic control (favouring the endo adduct) from thermodynamic control (favouring the more stable exo isomer) [6].



Scheme 2. Reaction of spilanthol with *p*-anisaldehyde.

Under catalyst-free conditions, no appreciable cycloaddition was detected, indicating that activation of the dienophile is required. This lack of reactivity is consistent with insufficient orbital overlap between the HOMO of spilanthol 1 and the LUMO of *p*-anisaldehyde and with an unfavourable HOMO–LUMO gap that hampers formation of the cycloaddition transition state [7].

To promote activation, several Lewis acids were screened—$AuCl_3$, $AlCl_3$, $AgSbF_6$, and $BF_3{\cdot}OEt_2$ (Table 1). Of these, only $BF_3{\cdot}OEt_2$ effectively delivered the Diels–Alder adducts, attributable to coordination at the aldehyde carbonyl, which stabilises the dienophile LUMO and narrows the HOMO–LUMO gap, thereby facilitating the transition state [8].

Table 1. Catalysts used in the synthesis.

Lewis Acid	Observation	Endo:Exo	Yield %
$AuCl_3$	No conversion	-	0
$AlCl_3$	No observable reaction	-	0
$Ag[SbF_6]$	No clear conversion	-	0
$BF_3{\cdot}OEt_2$		1:5	75

The purified compound obtained from the Diels–Alder reaction was characterized by proton nuclear magnetic resonance spectroscopy ([1]H-NMR) to determine its structural identity, as well as the spectral purity and integrity of the isolated cycloadduct. Figure 1 shows the [1]H-NMR spectrum of the compound recorded in chloroform at 400 MHz.

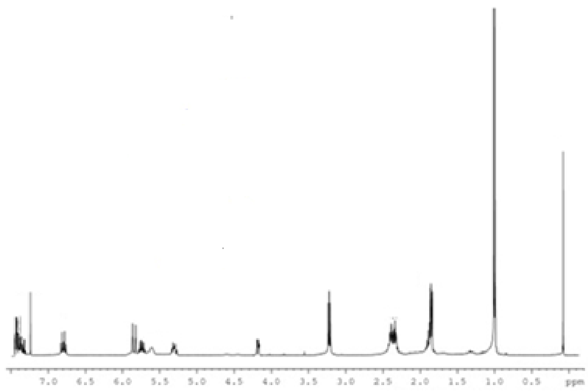


Figure 1. Proton nuclear magnetic resonance (^{1}H NMR) spectrum of the Diels-Alder Adduct recorded in deuterated chloroform ($CDCl_3$) at 400 MHz.

In the aliphatic region, signals were observed at δH 1.01 and 1.90 ppm, corresponding to methyl protons (–CH_3). An additional signal at δH 1.95 ppm was attributed to methylene protons (–CH_2–), while the resonance at δH 2.40 ppm was assigned to a methine proton (–CH–). Signals at δH 5.58, 5.75, 5.90, and 6.80 ppm were characteristic of olefinic protons (C=C). Finally, the signal at δH 7.40 ppm indicated the presence of aromatic protons. Collectively, these resonances support the proposed structure of the compound **2** as a pyran, a six-membered heterocyclic system composed of five carbon atoms and one oxygen atom, bearing an unsaturation (double bond) [9].

These findings are relevant for the synthesis of functionalized cyclohexene-type scaffolds, with potential applications in the development of bioactive compounds. Moreover, the fact that the reaction proceeds under mild conditions and employs acceptable solvents positions it as a strategy aligned with the principles of green chemistry, by enabling the formation of new molecular architectures without the need for intermediate steps or protecting groups [10].

4. Conclusions

Spilanthol **1** was successfully isolated and purified from the dried roots of *Heliopsis longipes*, and its structural identity was confirmed by proton nuclear magnetic resonance spectroscopy (^{1}H-NMR). Its reactivity as a diene in the Diels–Alder reaction was evaluated, showing that only p-anisaldehyde, in the presence of the Lewis acid catalyst $BF_3{\cdot}OEt_2$, enabled the formation of the desired cyclic adduct.

The study confirmed that the reaction proceeds through a hetero-Diels–Alder mechanism, as evidenced by the formation of a six-membered oxygen-containing ring, consistent with a pyran structure. Furthermore, both the yield and the stereoselectivity of the reaction were strongly influenced by the reaction conditions and the nature of the catalyst used.

These findings validate the use of Spilanthol **1** as a natural diene in cycloaddition reactions with synthetic potential, under conditions compatible with the principles of green chemistry. The developed methodology provides a solid foundation for the synthesis of structurally complex derivatives with potential biological activity.

Author Contributions: R.B.V.: methodology; M.M.A. & J.G.M.: Conceptualization; E.J.R., writing—review and editing. 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 financially supported by Secretaría de Ciencia, Humanidades, Tecnología e Innovación (SECIHTI) (Grant No. CBF-2025-I-2852). We also thank the Secretaría de Investigación y Posgrado/Instituto Politécnico Nacional (SIP/IPN) for their valuable support and resources.

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

References

1. Cilia-Lopez, V.G.; Aguirre-Rivera, J.R.; Reyes-Agüero, J.A.; Juárez-Flores, B.I. *Ethnobotany of Heliopsis longipes (Asteraceae: Heliantheae). Bol. Soc. Bot. Méx.* **2008**, *83*, 81–87.
2. Skolia, E.; Kokotos, C.G. Direct Diels-Alder Reaction of Biomass-Derived Furfurol with Maleimides in a Bio-Based Green Solvent. *EurJOC* **2024**, *27*, e202400105.
3. Abdul-Rahim, R.; Ayu-Jayusman, P.; Muhammad, N.; Mohamed, N.; Lim, V.; Hazwani Ahmad, N.; Mohamad, S.; Abdul-Hamid, Z.A.; Ahmad, F.; Mokhtar, N.; et al. Potential Antioxidant and Anti-Inflamatory Effects of Spilanthes acmella and Its Health Beneficial Effects: A Review. *Int. J. Environ. Res. Public Health* **2021**, *18*, 3532.
4. (a) Yasuda, I.; Takeya, K.; Itokawa, H. The geometric structure of spilanthol. *Chem. Pharm. Bull.* **1980**, *28*, 2251–2253; (b) Nakatani, N.; Nagashima, M. Pungent Alkamides from *Spilanthes acmella* L. *var. oleracea* Clarke. *Biosci. Biotechnol. Biochem.* **1992**, *56*, 759–762.
5. Alperth, F.; Erhart, S.; Kunert, O.; Bucar, F. Simple Green Purification of Spilanthol from Natural Deep Eutectic Solvent and Ethanolic *Acmella oleracea* (L.) R.K. Jansen Extracts Using Solid-Phase Extraction. *Separations* **2024**, *11*, 251.
6. Houk, K.N.; Liu, F.; Yang, Z.; Seeman, J.I. Evolution of the Diels-Alder Reaction Mechanism Since the 1930s: Woodward, Houk with Woodward, and the Influence of Computational Chemistry on Understanding Cycloadditions. *Angew. Chem. Int. Ed.* **2020**, *60*, 23.
7. Li, M.-Y.; Gu, A.; Li, J.; Liu, Y. Advanced green synthesis: Solvent-free and catalyst-free reaction. *Green Synth. Catal.* **2025**, *6*, 36–66.
8. Vermeeren, P.; Hamlin,T. A.; Fernéndez, I.; Bickelhaupt, F.M. How Lewis Acids Catalyze Diels-Alder Reactions Angew. *Chem. Int*. **2020**, *59*, 6201–6206.
9. Rashid, S.; Lone, W.I.; Rashid, A.; Bhat, B.A. Inverse electron demand Diels-Alder reaction in total synthesis of bioactive natural products. *Tetrahedron. Chem.* **2024**, *9*, 100066.
10. Raiol, A.; Pinheiro, M.; Belo, E.; Da Cunha, R.A.; Marinho, A.M.R.; Silva, S.Y.S.; Silva, S.C.; Andrade-Filho, T.; Gester, R. Experimental and Theoretical Spectroscopic Characterization, NLO Response, and Reactivity of the Pharmacological Agent Spilanthol and Analogues. *J. Mol. Struct.* **2021**, *1227*, 129423.

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.