

Short Note

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[Egar Pamela](#), Lukman Atmaja, [Mardi Santoso](#)*

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Short Note

Isoamyl (*E*)-3-(3,4-dimethoxyphenyl)acrylate

Egar Pamela, Lukman Atmaja and Mardi Santoso *

Department of Chemistry, Faculty of Science and Analytical Data, Institut Teknologi Sepuluh Nopember, Kampus ITS Sukolilo, Surabaya 60111, Indonesia

* Correspondence: tsv09@chem.its.ac.id

Abstract: Isoamyl (*E*)-3-(3,4-dimethoxyphenyl)acrylate (**1**) was obtained 95% yield by 2-methyl-6-nitrobenzoic anhydride (MNBA)/4-dimethylaminopyridine (DMAP)-catalyzed reaction at room temperature for 190 minutes in dichloromethane. The structure of isoamyl (*E*)-3-(3,4-dimethoxyphenyl)acrylate (**1**) was established by NMR, FTIR, and the high resolution of mass spectroscopies. *In vitro* sun protection factor evaluation exhibited value of 37.10 ± 0.03 which indicates that isoamyl (*E*)-3-(3,4-dimethoxyphenyl)acrylate (**1**) as a sunscreen agent with high protection.

Keywords: synthesis; isoamyl (*E*)-3-(3,4-dimethoxyphenyl)acrylate; sun protection factor

1. Introduction

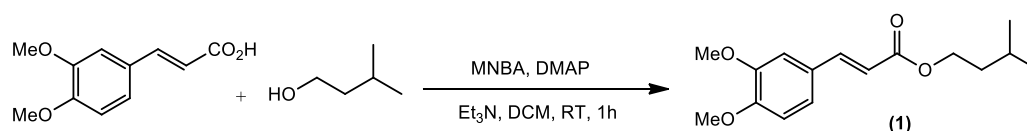
Cinnamate derivatives are widely used in cosmetics as fragrance [1], sunscreen [2], skin lightening [3] and anti-aging [4]. Esters of 4-methoxycinnamic acid namely isoamyl 4-methoxycinnamate and 2-ethoxyethyl 4-methoxycinnamate are compounds used in commercial sunscreens [5]. Photoprotection ability of sunscreen compounds can be enhanced by adding methoxy group to increase the coverage of protection [6]. Photoprotective efficiency of a sunscreen can be determined by the value of the sun protection factor [7]. Ester as cinnamate derivatives are generally synthesized by esterification involving thionyl chloride as a coupling agent, however thionyl chloride is included in the Chemical Weapons Convention list [8]. Synthesis of esters can also be carried out using *N,N'*-dicyclohexylcarbodiimide (DCC) and organocatalyst 4-dimethylaminopyridine (DMAP) as coupling agent [9]. However DCC is irritant, allergent, harm internal organs [10], and *N,N'*-dicyclohexylurea as its byproducts only moderately soluble in many organic solvents and insoluble in water resulting in a difficulty in purification [11]. On the other hand, the synthesis of carboxylic esters using 2-methyl-6-nitrobenzoic anhydride (MNBA) as a coupling can be carried out one pot at room temperature in high yields and good chemoselectivity [12]. Herewith, we reported MNBA/DMAP-catalyzed synthesis of isoamyl (*E*)-3-(3,4-dimethoxyphenyl)acrylate (**1**) and investigated their photoprotective ability by determining the SPF value.

2. Results and Discussion

2.1. Chemistry

Synthesis of isoamyl (*E*)-3-(3,4-dimethoxyphenyl)acrylate (**1**) involved reaction of 3,4-dimethoxycinnamic acid and isoamyl alcohol at room temperature in the presence of MNBA and DMAP in dichloromethane (Scheme 1). The crude product was purified by column chromatography to yield isoamyl (*E*)-3-(3,4-dimethoxyphenyl)acrylate (**1**) as a yellowish liquid in 95% yield. The ¹H NMR spectrum of the product confirmed the absence of the carboxylic proton signal of the 3,4-dimethoxycinnamic acid and showed the presence of isoamyl group signals. The ¹H NMR spectrum of the synthesis product confirmed the absence of the carboxylic proton signal of the 3,4-dimethoxycinnamic acid; and showed the presence of isoamyloxy group protons of the ester (**1**). The spectrum showed a doublet signal at a chemical shift (δ) 0.95 (J = 6.8 Hz) ppm was a signal of six protons from two methyl groups coupled to proton of the methine group which gave a multiplet signal at δ 1.72–1.74 ppm. A quartet signal at δ 1.60 (J = 6.8 Hz) ppm was the signal of two methylene

group protons coupled to two neighboring methylene group protons which gave a triplet signal at δ 4.23 ($J = 6.8$ Hz) ppm. A singlet signal at δ 3.91 ppm is the signal of six proton from the two methoxy groups, and a doublet signal at δ 6.30 ($J = 16.0$ Hz) ppm is the signal from an alkene proton coupled to a neighboring alkene proton which gave a doublet signal at δ 7.62 ($J = 16.0$ Hz) ppm. The aromatic protons gave two doublet signals at δ 6.86 ($J = 8.0$ Hz) and 7.05 ($J = 2.0$ Hz) ppm, also a doublet doublet signal at 7.10 ($J = 2.0; 8.0$ Hz) ppm. The ^{13}C spectrum showed fifteen signals corresponding to the number of carbon types present in compound **(1)**. Signals at δ 22.59 and 25.18 ppm were those of the methyl and methine carbon groups, respectively. Signals at δ 37.55 and 63.19 ppm respectively were signals of two methylene group carbons, and signals at δ 55.95 and 56.05 ppm are signals of two methoxy group carbons. The signals at δ 109.59, 111.06, 116.05, 122.68, 127.52, 144.57, 149.26, and 151.12 ppm were the signals of alkene and aromatic carbons. Signal at δ 167.43 ppm was the signal of the carbonyl ester carbon which was reinforced by the presence of strong absorption at wave number 1702 cm^{-1} in the infrared spectrum, and absorption at wave number 1157 cm^{-1} showed absorption of the C-O ester. The high-resolution mass spectrum further supported the synthesis product as isoamyl (*E*)-3-(3,4-dimethoxyphenyl)acrylate **(1)** by showing a peak ion $[\text{M}+\text{Na}]^+$ with the molecular formula $\text{C}_{18}\text{H}_{18}\text{O}_2\text{Na}$ at m/z 301.1418 which was almost the same as the calculation result of 301.1416.



Scheme 1. Synthesis of isoamyl (*E*)-3-(3,4-dimethoxyphenyl)acrylate **(1)**.

2.2. In Vitro Sun Protection Factor Evaluation

Sun protection factor (SPF) value indicates a quantitative measure of the effectiveness of a sunscreen formulation. SPF scoring is defined in four categories based on their protection abilities: low (SPF 6-14.9), moderate (SPF 15-29.9), high (SPF 30-50), and very high (SPF 50-100) [13]. Sunscreen agent with SPF value of 15 or more helps protect skin from UVA and UV B sun ultraviolet radiation, thereby further reducing the risk of skin cancer and premature skin aging [14]. SPF value was determined by the Mansur equation using spectrophotometry in the ultraviolet region at 290-320 nm [15]. Isoamyl (*E*)-3-(3,4-dimethoxyphenyl)acrylate **(1)** showed SPF value of 37.10 ± 0.03 in the range of 30-50 which indicates as a sunscreen agent with high protection. It was caused by the presence of aromatic ring conjugated with $\text{C}=\text{C}$ and $\text{C}=\text{O}$ group, and two methoxy group as auxochrome attached to the aromatic ring [16]. This compound has three possible mechanisms when exposed to UV photon energy: (i) conformational molecular changes; (ii) emission of radiation at longer wavelengths; or (iii) release of incident energy as heat [17,18]. When the molecules absorbed UV radiation, it causes the photoexcitation into a form that has higher energy. Cinnamates adopt a stable trans (*E*) form in the electronic ground state (S_0) which then isomerizes to the cis (*Z*) form. And when this molecule returns to its initial state, energy is emitted in a form that is lower than the energy absorbed so that it can provide sunscreen activity [19-21].

3. Materials and Methods

The chemicals and solvents were purchased from Sigma-Aldrich (St. Louis, MO, USA), Merck (Rahway, NJ, USA), and Fluka (Charlotte, NC, USA) and were used without further purification. Thin layer chromatography was carried out on Merck 0.20 mm precoated silica gel aluminum plates (Kieselgel 60, F254) and was visualized using a UV lamp at 245 nm. Dry column flash chromatography was carried out on Merck 60H. Nuclear Magnetic Resonance spectra were obtained in CDCl_3 on a Jeol JNM-ECS400 spectrometer (400 MHz). A high-resolution mass spectrum was recorded on a Thermo Scientific TSQ Vantage Triple State Quadrupole, and an infrared spectrum was obtained on a Shimadzu 8400S FTIR spectrophotometer.

3.1. Synthesis of isoamyl (*E*)-3-(3,4-dimethoxyphenyl)acrylate (**1**)

A solution of 3,4-dimethoxycinnamic acid (0.31 g, 1.50 mmol), DMAP (0.018 g, 0.15 mmol), MNBA (0.62 g, 1.80 mmol) and triethylamine (0.46 mL, 3.30 mmol) in dichloromethane (15 mL) was stirred for 10 min at room temperature. Isoamyl alcohol (0.16 mL; 1.50 mmol) was then added, and the solution was stirred further for an additional 190 minutes (the reaction was monitored by TLC with ethyl acetate/*n*-hexane (1/2) eluant. The solvent was removed under reduced pressure, and the crude product was purified using “dry-column” flash column chromatography with ethyl acetate/*n*-hexane (1/20) eluant to afford isoamyl (*E*)-3-(3,4-dimethoxyphenyl)acrylate (**1**) as a yellowish liquid (0.40 g, 95%). ¹H NMR (400 MHz, CDCl₃) δ 0.95 (d, *J* = 6.8 Hz, 6H); 1.60 (q, *J* = 6.8 Hz, 2H); 1.72-1.74 (m, *J* = 6.8 Hz, 1H); 3.91 (s, 6H); 4.23 (t, *J* = 6.8 Hz, 2H); 6.30 (d, *J* = 16.0 Hz, 1H); 6.86 (d, *J* = 8.0 Hz, 1H); 7.05 (d, *J* = 2.0 Hz, 1H); 7.10 (dd, *J* = 2.0; 8.0 Hz, 1H); 7.62 (d, *J* = 16.0 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃) δ 22.59, 25.18, 37.55, 55.95, 56.05, 63.19, 109.59, 111.06, 116.05, 122.68, 127.52, 144.57, 149.26, 151.12, 167.43. FTIR (KBr) ν (cm⁻¹) 1702 (C=O ester), 1157 (C-O ester). HRESIMS *m/z* (pos): 301.1418 C₁₈H₁₈O₂Na (calcd. 301.1416) (Supplementary Materials).

3.3. In Vitro Sun Protection Factor Determination

Determination of sun protection factor (SPF) value of isoamyl (*E*)-3-(3,4-dimethoxyphenyl)acrylate (**1**) was carried out by the ultraviolet-visible spectrophotometry method described by Mansur et al. [15]. Solution of compound (**1**) was prepared at a concentration of 1 mg.mL⁻¹ in 96% ethanol, then the absorbance was measured at 290-320 nm. SPF values were determined using Equation (1):

$$\text{SPF} = \text{CF} \times \sum_{290}^{320} \text{EE}(\lambda) \times I(\lambda) \times \text{Abs}(\lambda) \quad (1)$$

where CF stands for correction factor (10); EE(λ) is the erythemogenic effect of wavelength radiation (λ); I(λ) is the intensity of solar radiation in the wavelength (λ); and Abs(λ) is the spectrophotometry reading of the absorbance of sunscreen solution in the wavelength (λ).

5. Conclusions

Isoamyl (*E*)-3-(3,4-dimethoxyphenyl)acrylate (**1**) was successfully synthesized through MNBA/DMAP-mediated esterification in 95% yield. Compound (**1**) exhibited SPF value of 37.10 ± 0.03 in the range of 30-50 which indicates as a sunscreen agent high protection.

Supplementary Materials: The following supporting information can be downloaded online, Figure S1: IR spectrum of compound (**1**); Figure S2: ¹H NMR spectrum of compound (**1**); Figure S3: ¹³C NMR spectrum of (**1**); Figure S4: High Resolution Mass spectrum of compound (**1**).

Author Contributions: Conceptualization, M.S.; methodology, M.S., E.P.; software, E.P.; validation, M.S., L.A.; formal analysis, E.P.; investigation, E.P.; resources, M.S.; data curation, M.P.; writing—original draft preparation, E.P.; writing—review and editing, M.S., L.A.; visualization, E.P.; supervision, M.S.; project administration, M.S.; funding acquisition, M.S. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement: The data presented in this study are available in the Supplementary Materials.

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

References

1. Steele, J. H.; Bozor, M. X.; Boyce, G. R. Transmutation of Scent: An Evaluation of the Synthesis of Methyl Cinnamate, a Commercial Fragrance, via a Fischer Esterification for the Second-Year Organic Laboratory. *J. Chem. Educ.* **2020**, 97, 11, 4127–4132, doi.org/10.1021/acs.jchemed.0c00861.
2. Wong, N.G.K.; Dessent, C.E.H. Illuminating the Effect of the Local Environment on the Performance of Organic Sunscreens: Insights From Laser Spectroscopy of Isolated Molecules and Complexes. *Front. Chem.* **2022**, 9, 812098, doi: 10.3389/fchem.2021.812098.
3. Tang, K.; Jiang, Y.; Zhang, H.; Huang, W.; Xie, Y.; Deng, C.; Xu, H.; Song, H.; Xu, H. Design, synthesis of Cinnamyl-paeonol derivatives with 1, 3-Dioxypopyl as link arm and screening of tyrosinase inhibition activity in vitro. *Bioorg. Chem.* **2021**, 106, 104512, doi: 10.1016/j.bioorg.2020.104512.
4. Park, P. J., & Cho, E.G. Kojyl Cinnamate Ester Derivatives Increase Adiponectin Expression and Stimulate Adiponectin-Induced Hair Growth Factors in Human Dermal Papilla Cells. *Int. J. Mol. Sci.* **2019**, 20(8), 1859, doi: 10.3390/ijms20081859.
5. Ma, Y.; Yoo, J. History of sunscreen: An updated view. *J. Cosmet. Dermatol.* **2021**, 20(4), 1044-1049, doi: 10.1111/jocd.14004.
6. Martincigh, B. S.; Ollengo, M. A. The Photostabilizing Effect of Grape Seed Extract on Three Common Sunscreen Absorbers. *J. Photochem. Photobiol.* **2016**, 92(6), 870–884, doi:10.1111/php.12652
7. Solano, F. Photoprotection and Skin Pigmentation: Melanin-Related Molecules and Some Other New Agents Obtained from Natural Sources. *Molecules* **2020**, 25(7), 1537, doi:10.3390/molecules25071537
8. Kuitunen, M.-L.; Cecilia Altamirano, J.; Siegenthaler, P.; Hannele Taure, T.; Antero Häkkinen, V.; Sinikka Vanninen, P. Derivatization and rapid GC-MS screening of chlorides relevant to the chemical weapons convention in organic liquid samples. *Anal. Methods* **2020**, 12, 2527–2535, doi: 10.1039/D0AY00263A.
9. Amini, N.; Handayani, S.; Hudiyono, S. Toxicity test using brine shrimp lethality test (BSLT) and antioxidant assay of ricinoleic acid-based ester conjugate synthesized by Steglich esterification. *AIP Conf. Proc.* **2022**, 2638(1), 070012. doi: 10.1063/5.0104219.
10. Han, S.Y.; Kim, Y.A. Recent Development of Peptide Coupling Reagents in Organic Synthesis. *Tetrahedron* **2004**, 60, 2447-2467, doi: 10.1016/j.tet.2004.01.020
11. Jordan, A.; Whymark, K.D.; Sydenham, J.; Sneddon, H.F. A Solvent-Reagent Selection Guide for Steglich-Type Esterification of Carboxylic Acids. *Green. Chem.* **2021**, 23, 6405-6413, doi: 10.1039/D1GC02251B.
12. Shiina, I.; Nakata, K. The first asymmetric esterification of free carboxylic acids with racemic alcohols using benzoic anhydrides and tetramisole derivatives: An application to the kinetic resolution of secondary benzylic alcohols. *Tetrahedron Lett.* **2007**, 48, 8314–8317, doi: 10.1016/j.tetlet.2007.09.135.
13. Manaia, E. B.; Kaminski, R. C. K.; Corrêa, M. A.; Chiavacci, L. A. Inorganic UV filters. *Braz. J. Pharm. Sci.* **2013**, 49(2), 201–209. doi: 10.1590/s1984-82502013000200002
14. Facts about Sunscreen. Available online: <https://www.fda.gov/news-events/rumor-control/facts-about-sunscreen> (accessed on 5 July 2023).
15. Mansur, J.d.S.; Breder, M.N.R.; Mansur, M.C.d.A. Determinação do fator de proteção solar por espectrofotometria. *An. Bras. Dermatol.* **1986**, 61, 121–124.
16. Gunia-Krzyżak, A.; Słoczyńska, K.; Popiół, J.; Koczurkiewicz, P.; Marona, H.; Pękala, E. Cinnamic acid derivatives in cosmetics: current use and future prospects. *Int. J. Cosmet. Sci.* **2018**, 40(4), 356–366. doi: 10.1111/ics.12471.
17. Antoniou, C.; Kosmadaki, M.G.; Stratigos, A.J.; Katsambas, A.D. Sunscreens – what’s important to know. *J. Eur. Acad. Dermatol. Venereol.* **2008**, 22(9), 1110- 1118, doi: 10.1111/j.1468-3083.2007.02580.x.
18. Kiss, B.; Bíró, T.; Czifra, G.; Tóth, B.; Kertész, Z.; Szikszai, Z.; Kiss, A.Z.; Juhász, I.; Zouboulis, C.C.; Hunyadi, J. Investigation of micronized titanium dioxide penetration in human skin xenografts and its effect on cellular functions of human skin-derived cells. *Exp. Dermatol.* **2008**, 17(8), 659-667, doi: 10.1111/j.1600-0625.2007.00683.x.
19. Kinoshita, S.; Harabuchi, Y.; Inokuchi, Y.; Maeda, S.; Ehara, M.; Yamazaki, K.; Ebata, T. Substitution effect on the nonradiative decay and trans → cis photoisomerization route: a guideline to develop efficient cinnamate-based sunscreens. *Phys. Chem. Chem. Phys.* **2021**, 23(2), 834–845. doi:10.1039/d0cp04402d.

20. Dalton J.; Richings G.W.; Woolley J.M.; Abiola T.T.; Habershon S.; Stavros V.G. Experimental and Computational Analysis of Para-Hydroxy Methylcinnamate following Photoexcitation. *Molecules* **2021**, 26(24), 7621. doi: 10.3390/molecules26247621.
21. Chang, X.P.; Li, C.X.; Xie, B.B.; Cui, G. Photoprotection Mechanism of p-Methoxy Methylcinnamate: A CASPT2 Study. *J. Phys. Chem* **2015**, 119(47), 11488–11497. doi:10.1021/acs.jpca.5b08434.

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