chemistry proceedings

MDPI

Proceeding Paper

Aryl Itaconic Acids from Aryl Aldehydes and (Triphenylphosphoranylidene)succinic Anhydride by a One Pot Ring Opening—Wittig Olefination—Hydrolysis Reaction †

Vijo Polouse [1], Salama Almheiri [1], Noura Alwahedi [1], Arwa Alzeyoudi [1], Maryam Aghaei [1], Sreeraj Gopi [2,3] and Thies Thiemann [1,*]

[1] Department of Chemistry, College of Science, United Arab Emirates University, Al Ain PO Box 15551, United Arab Emirates; vijo.p@uaeu.ac.ae (V.P.); 202000554@uaeu.ac.ae (S.A.); 201916649@uaeu.ac.ae (N.A.); 201906705@uaeu.ac.ae (A.A.); 201721360@uaeu.ac.ae (M.A.)
[2] Molecules Biolabs, Kinfra, Koratty, Kerala, India
[3] Faculty of Chemistry, Gdansk University of Technology, Gdansk, Poland
* Correspondence: thies@uaeu.ac.ae; thiesthiemann@yahoo.de
† 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: (Triphenylphosphoranylidene)succinic anhydride, which is prepared from triphenylphosphine and maleic anhydride and is itself not reactive towards aryl aldehydes, is ring opened with methanol to methyl (triphenylphosphoranylidene)succinate. In one pot, the newly formed phosphorane is reacted with aryl aldehydes to methyl aryl itaconates, which are subsequently hydrolyzed with aqueous sodium hydroxide to aryl itaconic acids. The biological activity of 12 aryl itaconic acids thus prepared against 4 g-positive and 4 g-negative bacterial strains has been studied.

Keywords: itaconic acids; one pot synthesis; Wittig reaction; anti-bacterial studies

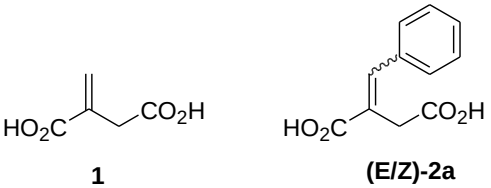
Citation: Polouse, V.; Almheiri, S.; Alwahedi, N.; Alzeyoudi, A.; Aghaei, M.; Gopi, S.; Thiemann, T. Aryl Itaconic Acids from Aryl Aldehydes and (Triphenylphosphoranylidene)succinic Anhydride by a One Pot Ring Opening—Wittig Olefination—Hydrolysis Reaction. *Chem. Proc.* **2024**, *6*, x. https://doi.org/10.3390/xxxxx

Academic Editor(s): Name

Published: 15 November 2024

1. Introduction

Itaconic acid (**1**) (Figure 1) is a fatty acid that is produced by macrophages and monocytes in various organisms under stress response as well as by certain myeloid-derived suppressor cells [1]. It is a side product of the Krebs cycle. Thus, some cells upon experiencing stress, suppress the tricarboxylic acid cycle, and this is when the metabolite *cis*-aconitate starts accumulating. The enzyme aconitate decarboxylase (ACOD1) metabolizes the excess *cis*-aconitate to itaconate. Itaconic acid and some of its ester derivatives are known as immunoregulators, limiting inflammation. Also, the compounds have an effect on bacterial and viral infections.



1 **(E/Z)-2a**

Figure 1. Itaconic acid (1) and (E/Z)-phenyl itaconic acid.

Both *E*- and *Z*-isomers of phenyl itaconic acid (**2a**) (Figure 1) have been isolated as metabolites from bacterial strains such as from *Azoarcus tolulyticus* [2]. Also, *E*-phenyl itaconic acid has been found as a constituent of *Artemisia argyi* (Levl and Vant) [3]. Aryl itaconic acids are usually prepared by Stobbe-type reaction of aryl aldehydes with dialkyl

succinate [4,5] with subsequent ester hydrolysis. The products of the Stobbe-type reaction are often *Z*-configurated, but mixtures of *E*- and *Z*-configurated compounds are also known. In the following, a Wittig route to E-aryl itaconic acids is pursued. The biological activities of the *E*-aryl itaconic acids were to be assayed, initially against 4 g-positive and 4 g negative bacterial strains.

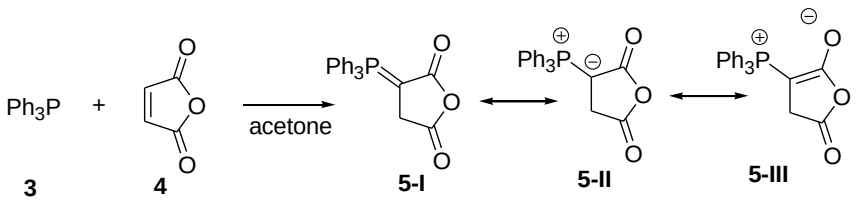
2. Materials and Methods

2.1. General—Chemical Preparation

Infrared spectroscopy was carried out on a Perkin Elmer Spectrum Two FT-IR spectrometer. Samples were measured as KBr pellets. ^{1}H and ^{13}C NMR spectra were recorded with a Varian 400 NMR (^{1}H at 395.7 MHz, ^{13}C at 100.5 MHz) spectrometer in DMSO-d^6 and $CDCl_3$ as solvents. The chemical shifts (δ) were reported in ppm and were referenced to the residual protonated solvent, e.g., δ = 2.49 ppm for DMSO-d^6). Coupling constants (J) are given in Hz. Proton multiplicity was assigned using the following abbreviations: Singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m). Additionally, the abbreviation for broad (br) was used. Mass spectra were measured on a Shimadzu LCMS-8045 with an electrospray ionization (ESI) ion source, using a mobile phase of acetonitrile and 0.1% formic acid buffer in a 70/30 ratio, with a flow rate of 0.5 mL/min under isocratic elution, where a C18 column (150 × 2 mm) was used. Column chromatography was carried out on recycled [6] silica gel (60 Å, 230–400 mesh, Sigma-Aldrich). Analytical thin layer chromatography (TLC) was carried out on silica on TLC Alu foils from Fluka (with fluorescent indicator at λ = 254 nm).

Aryl aldehydes, alkyl iodides (CH_3I and C_2H_5I), triphenyl phosphine, maleic anhydride, conc. hydrochloric acid, methanol, ethanol, acetone, sodium methoxide, sodium hydroxide and potassium hydroxide were acquired commercially and used without further purification. 2-Methoxybenzaldehyde (from salicylaldehyde), 3-ethoxy-4-methoxybenzalde- hyde (from 3-hydroxy-4-methoxybenzaldehyde) and 2,4-dimethoxybenzaldehyde (from 2,4-dihydroxybenzaldehyde) and 4-ethoxy-3-methoxybenzaldehyde (from 4-hydroxy-3-methoxybenzaldehyde [vanillin]) were prepared by alkylation of the respective phenols (KOH, CH_3I or C_2H_5I, DMSO) analogous to a known procedure [7].

Triphenylphosphoranylidene)succinic anhydride (**5**) was obtained from the reaction of triphenylphosphine (**3**) and freshly sublimated maleic anhydride (**4**) in acetone as solvent according to a known procedure (Scheme 1) [8].



Hudson and Chopard 1963

Scheme 1. Preparation of (triphenylphosphoranylidene)succinic anhydride (**5**) [8].

2.2. Experimental—Chemical Synthesis

Procedure: (*E*)-2-(2,5-Dimethoxyphenyl)methylenebutane-1,4-doic acid (**2b**).—Phosphorane (**5**) (2.50 g, 6.94 mmol) was stirred in MeOH (20 mL) at rt for 10 h. Thereafter, the red-orange solution was cooled to 0 °C, and solid sodium methoxide (NaOMe, 390 mg, 7.22 mmol) and immediately thereafter 2,5-dimethoxybenzaldehyde (**9b**, 1.13 g, 6.80 mmol) were added. The resulting solution was stirred at rt for 1.5 h, thereafter it was stirred under reflux for 6 h. The solution was re-cooled to rt, and a solution of aq. NaOH (2.0 g in 30 mL H_2O) was added. The resulting mixture was stirred for 3 h at 65 °C. Thereafter, the mixture was cooled to rt and extracted with CH_2Cl_2 (3 × 20 mL). The basic aq.

phase was cooled to 0 °C and acidified with half conc. HCl. Crystallization of the product sets in with the acidified phase cooled to 0 °C. Crystallization can continue for an extended amount of time. The last two purification steps should be carried out at speed as otherwise crystallization can occur in the organic phase as well as the interphase. In products where crystallization does not occur readily, the acidified organic phase can be extracted with CH_2Cl_2. Then, the organic phase is dried over $MgSO_4$ and concentrated *in vacuo*. **2b** (760 mg, 42%) is obtained as a colorless solid, mp. 175–176 °C [Lit. 173–175 °C [9]]; IR (KBr, ν_{max}) 3450–2550 (OH), 2921, 2851, 1702, 1680, 1504, 1233, 1221, 1048, 1019 cm^{-1}. ^1H NMR (400 MHz, DMSO-d^6) δ 12.46 (br, 2H), 7.71 (s, 1H), 6.97 (d, 1H, ^3J = 8.8 Hz), 6.93 (dd, 1H, ^3J = 8.8 Hz, ^4J = 2.8 Hz), 6.80 (d, 1H, ^4J = 2.8 Hz), 3.71 (s, 3H, OCH_3), 3.65 (s, 3H), 3.25 (s, 2H, CH_2) ppm. ^{13}C NMR (100 MHz, DMSO-d^6) δ 172.8 (CO_2H), 168.7 (CO_2H), 153.0, 151.7, 136.3, 127.7, 124.4, 115.6, 115.1, 112.5, 56.2 (OCH_3), 55.7 (OCH_3), 34.1 (CH_2) ppm. MS (*m*/*z*, *ESI*) 265 $[M\text{-}H]^+$.

2.3. Antibacterial Assay—Methodology

All the bacterial cultures were obtained from the microbial collection center, IMTECH Chandigarh, India. Active cultures of the four gram positive bacteria *Staphylococcus aureus* MTCC3160, *Staphylococcus lentus* MTCC 2292, *Bacillus cereus* MTCC6629, *Bacillus subtilis* MTCC1305 and the four gram negative bacteria *Pseudomonas aeruginosa* MTCC1748, *Pseudomonas putida* MTCC 2492, *Escherichia coli* MTCC 1554, and *Klebsiella pneumoniae* MTCC 3040 were used. Streptomycin (50 μg/mL) was used as a standard.

2.4. Antibacterial Assay—Experimental

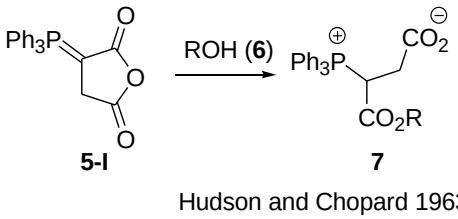
A single bacterial colony of a pure culture was transferred to a 150 mL conical flask containing 50 mL nutrient broth media and incubated at 37 °C for 8–12 h. All the samples were dissolved in 1 mL DMSO and made into aliquots of different concentrations for minimum inhibitory concentration (MIC) assay. The antibacterial assay was carried out by performing the swab streak method. For this, nutrient agar media was prepared and sterilized at 121 °C with 15 lbs. pressure for 15 min. The sterile media was poured into petri dishes and allowed to solidify. A sterile cotton swab was taken, and the culture was uniformly spread onto the nutrient agar surface. Active bacterial cultures were taken and 100 μL of culture were added onto the agar surface. After the plates were solidified, wells were made using sterile well borer, and samples were loaded, 100 μL each, into the wells, respectively. Plates were incubated at 37 °C for 18–24 h. in a bacterial incubator. The bacterial plates were observed after the incubation period.

4. Results and Discussion

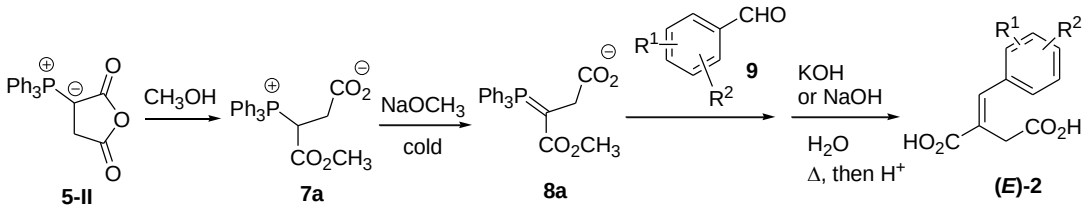
4.1. Wittig Olefination-Preparation of Aryl Itaconic Acids

(Triphenylphosphoranylidene)succinic anhydride (**5**) can prepared easily by the reaction of triphenylphosphine (PPh_3, **3**) with maleic anhydride (**4**) (Scheme 1) [8]. **5** undergoes Wittig olefination reaction only with the most reactive ketones and aldehydes such as chloral [8]. It does, however, ring-open in the presence of alcohols to provide **7** such as **7a** (Scheme 2). Adding a base such as sodium methoxide to **7a** creates phosphorane **8a**. **8a** undergoes a Wittig reaction when aryl aldehydes (**9**) are present to give monoalkyl aryl itaconates as *E*-isomers, which can be subjected directly to base catalyzed hydrolysis by the addition of either aq. NaOH and aq. KOH, providing (*E*)-aryl itaconic acids (**2**), in one pot from maleic anhydride (**4**) (Scheme 3). Here, it needs to be said that **7** is prone to a thermal fragmentation reaction to acrylates, which has been used in the synthesis of alkyl acrylates from maleic anhydride in the presence of triphenylphosphine (**3**) and an alcohol (**6**) [10] (Scheme 4) and in the synthesis of Michael adducts of such acrylates with aryl thiols **11** such as in the synthesis of aryl 3-thioarylthiopropionate **12** (Scheme 5) [11]. It is because of this that the addition of sodium methoxide to **7a** in the featured reaction (Scheme 3) has to be performed carefully at 0 °C. Thereafter, the reaction is stirred at rt

and only at the end the temperature is raised to 65 °C for 6 h. Hydroylsis of the formed methyl aryl itaconates is carried out in situ with the addition of an aq. solution of NaOH or KOH. For the purification of the product, the reaction mixture is diluted with water, and all side products, including triphenylphosphine oxide are extracted with CH_2Cl_2. Thereafter, the aq. phase is carefully acidified, where in most instance the aryl itaconic acids will crystallize slowly. Where this does not happen, the aqueous phase is extracted with CH_2Cl_2, the organic phase dried over $MgSO_4$ and subsequently evaporated to give the solid aryl itaconic acids with can be washed with a small amount of diethyl ether. The aryl itaconic acids thus obtained with their respective yields are shown in Figure 2.



Scheme 2. Alcoholysis of (triphenylphosphoranylidene)succinic anhydride (**5**) [8].



Scheme 3. One-pot reaction of (triphenylphosphoranylidene)succinic anhydride (**5**) to (E)-aryl itaconic acids **(*E*)-2** [as the main feature of this contribution].

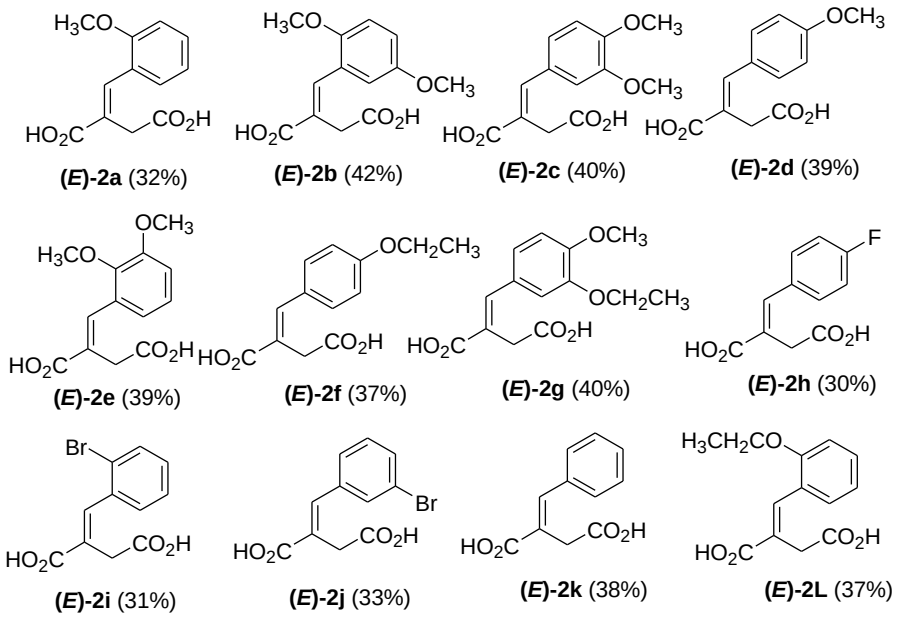
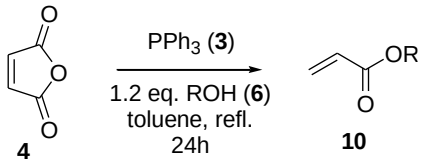
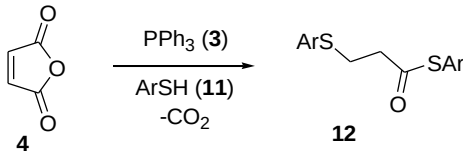


Figure 2. Aryl itaconic acids produced utilizing the synthetic route shown in Scheme 3. Yields are shown in brackets.



G. Adair et al. 2003

Scheme 4. Fragmentation reaction of intermittent (triphenylphosphoranylidene)succinic anhydride (**5**) to acrylates **10** as a side reaction to the Wittig olefination, discussed in this contribution [9].



N. Nowrouzi et al. 2023

Scheme 5. Fragmentation reaction of intermediately formed (triphenylphosphoranylidene)succinic anhydride (**5**) to thioacrylates with subsequent Michael addition [10].

4.2. Antibacterial Activity of the Synthesized Compounds

The impact of 12 synthesized aryl itaconic acids on four gram-positive bacterial pathogen *S. aureus*, *S. lentus*, *B. cereus*, and *B. subtilis* was studied using the swab streak method. After the incubation period, the bacterial plates were observed. 2-(3-Ethoxy-4-methoxyphenyl)methylenebutane-1,4-dioic acid (***E*-2g**) and 2-(2-bromophenyl)methylenebutane-1,4-dioic acid (***E*-2j**) showed activity against all four gram-positive bacterial pathogens, while 2-(2,5-dimethoxyphenyl)methylenebutane-1,4-dioic acid (***E*-2b**) and 2-(2,3-dimethoxyphenyl)methylenebutane-1,4-dioic acid (***E*-2e**) showed activity against only two pathogen strains *S. aureus* and *S. lentus*. The results are summarized in Table 1 and Figure 3.

Sample Name	Gram Negative Bacterial pathogens			
	P. aeruginosa	P. putida	E. coli	K. pneumoniae
(E)-2a	No activity	No activity	No activity	No activity
(E)-2b	12mm	10mm	No activity	No activity
(E)-2c	No activity	No activity	No activity	No activity
(E)-2d	No activity	No activity	No activity	No activity
(E)-2e	12mm	14mm	No activity	No activity
(E)-2f	No activity	No activity	No activity	No activity
(E)-2g	10mm	10mm	08mm	10mm
(E)-2h	No activity	No activity	No activity	No activity
(E)-2i	10mm	12mm	10mm	10mm
(E)-2j	No activity	No activity	No activity	No activity
(E)-2k	No activity	No activity	No activity	No activity
(E)-2L	No activity	No activity	10mm	10mm
Standard	14mm	14mm	14mm	16mm

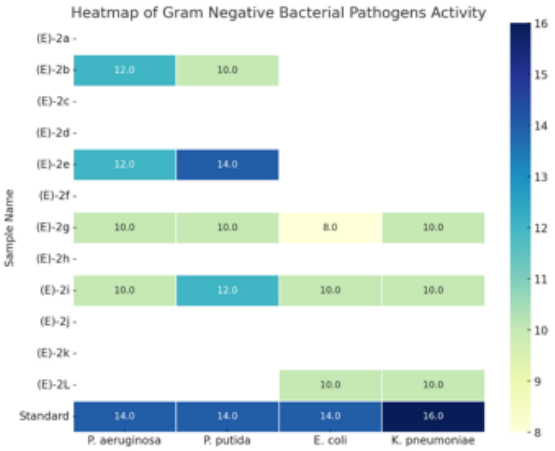


Table 1. and **Figure 3**. Antibacterial activity of compounds **2a–2L** against gram-positive pathogens.

Sample Name	Gram Negative Bacterial pathogens			
	P. aeruginosa	P. putida	E. coli	K. pneumoniae
(E)-2a	No activity	No activity	No activity	No activity
(E)-2b	12mm	10mm	No activity	No activity
(E)-2c	No activity	No activity	No activity	No activity
(E)-2d	No activity	No activity	No activity	No activity
(E)-2e	12mm	14mm	No activity	No activity
(E)-2f	No activity	No activity	No activity	No activity
(E)-2g	10mm	10mm	08mm	10mm
(E)-2h	No activity	No activity	No activity	No activity
(E)-2i	10mm	12mm	10mm	10mm
(E)-2j	No activity	No activity	No activity	No activity
(E)-2k	No activity	No activity	No activity	No activity
(E)-2L	No activity	No activity	10mm	10mm
Standard	14mm	14mm	14mm	16mm

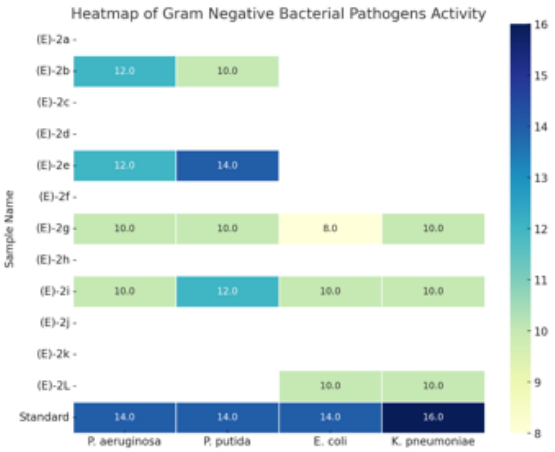


Table 2. and **Figure 4**. Antibacterial activity of compounds **2a–2L** against gram-negative pathogens.

Supplementary Materials: Available upon request.

Author Contributions: Conceptualization, V.P. and T.T.; methodology, V.P. and T.T.; investigation, V.P., S.A., N.A., A.A., M.A., T.T.; resources, T.T.; data curation, V.P., S.G., T.T.; writing—original draft preparation, V.P., T.T.; writing—review and editing, V.P., S.G., T.T.; supervision, T.T. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Additional data is available on request.

Acknowledgments: The authors thank Kalams Institute of Sciences, Hyderabad, India, for the biological activity studies of compounds **2a–2L**.

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

References

1. Zhao, H.; Teng, D.; Yang, L.; Xu, X.; Chen, J.; Jiang, T.; Feng, A.Y.; Zhang, Y.; Frederick, D.T.; Gu, L.; et al. Myeloid-derived itaconate suppresses cytotoxic CD8+ T cells and promotes tumour growth. *Nature Metabol.* **2022**, *4*, 1660–1673.
2. Migaud, M.E.; Chee-Sanford, J.-C.; Tiedje, J.M.; Frost, J.W. Benzylfumaric, benzylmaleic, and Z- and E-phenylitaconic acids: Synthesis, characterization, and correlation with a metabolite generated by *Azoarcus tolulyticus* Tol-4 during anaerobic toluene degradation. *Appl. Environ. Microbiol.* **1996**, *62*, 974–978.
3. Lao, A.; Fujimoto, Y.; Tatsuno, T. Studies on the constituents of *Artemisia argyi* Levl and Vant. *Chem. Pharm. Bull.* **1984**, *32*, 723–727.
4. Rao, K.R.; Bagavant, G. Stobbe condensation. Formation of fulgenic and itaconic acids. *Indian J. Chem.* **1969**, *7*, 859–861.
5. Wang, Y.; Zhong, Z.; Wu, G.; Chang, Y. Design, synthesis and hypoglycemic activity of α-benzylsuccinic acid derivatives. *Yaoxue Xuebao* **2009**, *44*, 491–495.
6. Bankole, A.A.; Poulose, V.; Ramachandran, T.; Hamed, F.; Thiemann, T. Comparative study of the selective sorption of organic dyes on inorganic materials—A cost-effective method for waste treatment in educational and small research laboratories. *Separations* **2022**, *9*, 144.
7. Johnstone, R.A.W.; Rose, M.E. A rapid, simple, and mild procedure for alkylation of phenols, alcohols, amides and acids. *Tetrahedron* **1979**, *35*, 2169–2173.
8. Hudson, R.F.; Chopard, P.A. Structure et reactions du compose d'addition: Triphenylphosphine—Anhydride maléique. *Helv. Chim. Acta* **1963**, *46*, 2178–2185.
9. Kulkarni, A.B.; Pandit, A.L.; Shroff, H.D.; Hosangadi, B.D.; Katrak, M.N.; Diwadkar, A.B.; Ginde, B.S. Conformational analysis. I. Stereochemistry of itaconic acids. *Indian J. Chem.* **1964**, *2*, 443–448.

10. Adair, G.R.A.; Edwards, M.G.; Williams, J.M.J. Triphenylphosphine-catalysed conversion of maleic anhydride into acrylate esters. *Tetrahedron Lett.* **2003**, *44*, 5523–5525.
11. Nowrouzi, N.; Abbasi, M.; Zellifard, Z. Ph_3P-mediated decarboxylative ring-opening of maleic anhydride by thiolic compounds: Formation of two carbon–sulfur bonds. *RSC Adv.* **2023**, *13*, 9242–9246.