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Communication

Parallel Synthesis of Aurones Using a Homogeneous Scavenger

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Abstract: The ability to synthesize arrays of related compounds quickly and with good purity has become critical for a rapid exploration of their properties for biological or material applications. While a number of methods have been developed to enable this combinatorial synthesis, the existing options were not readily appliable to the synthesis of aurones using the simple Knoevenagel condensation approach. In order to avoid the time, expense, and lowered yields associated with flash column chromatography, we developed a scavenging approach for their synthesis. This method uses an excess of aldehyde to ensure complete conversion to aurones, followed by selective removal of the remaining aldehyde using a simple, inexpensive scavenger – isoniazid – and subsequent extraction with dilute acid, to produce the desired compounds with good purity under operationally simple conditions. This approach is expected to be applicable to many other reactions involving aldehydes as one of the reactants.

Keywords: solid support; library synthesis; chromatography-free; homogeneous synthesis

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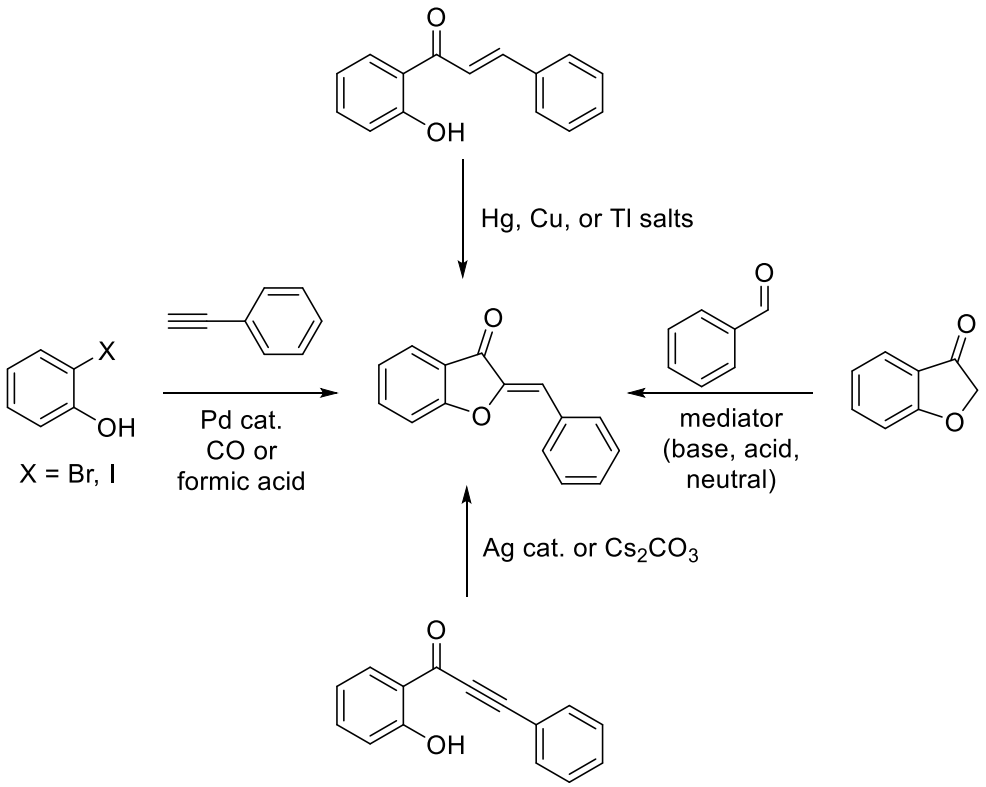
1. Introduction

First isolated from the petals of yellow flowering plants over 60 years ago, aurones have remained a largely neglected sub-family of the flavonoid family of natural products [1]. Only in more recent years has greater interest been focused on aurones, noting a wide range of biological activity, including anti-cancer, anti-fungal, anti-parasitic, and anti-inflammatory activity [2,3]. Efforts from our group in particular have expanded this study to aurone analogs with simple unsubstituted benzofuranones, and have demonstrated significant activity in the fungal and inflammatory areas as well as their optical properties [4–8].

Part of the reason for the limited and slow exploration of aurones doubtless has to do with aurones being present in very small quantities in natural sources and, indeed, not being the most thermodynamically stable of the flavonoid frameworks. In fact, the aurone base scaffold is quite unusual, consisting of a 15-carbon skeleton containing a benzofuranone linked via an exocyclic alkene to an aromatic ring [9]. This unusual ring system has attracted the attention of synthetic chemists, with various methods having been developed to access this framework. The most common ways to synthesize aurones fall into three main categories (Scheme 1). An early option was the cyclization of chalcones, usually in the presence of copper, mercury, or thallium salts [10,11]. While chalcones can be easily accessed, most of these reactions use mercury salts and generate stoichiometric toxic mercury waste, and can be very substrate-dependent in terms of their efficiency. A more recent alternative involves the cyclization of ynoylphenols in the presence of silver catalysts or cesium carbonate [12,13]. A related option is the carbonylative cyclization of ortho-iodophenols with carbon monoxide and alkynes in the presence of a palladium catalyst [14,15]. The advantages of these two methods are that they are catalytic and avoid mercury, and that the starting substrates are still readily available. A further frequently employed option is Knoevenagel condensation of a benzofuranone with an aldehyde. This option is the most frequently used, and numerous variations have been developed,

including those with basic conditions [16], acidic conditions [17], and largely neutral conditions [18–21]. It is simple and frequently high-yielding, and many benzofuranones are commercially available, while others can be readily prepared using standard Friedel–Crafts approaches from phenols.



Scheme 1. Main routes to aurones.

In examining these approaches, one clear aspect is that they are all entirely solution phase methods, with each compound synthesized requiring purification (most frequently via column chromatography) prior to assessing their biological activity. In our experience, purification on silica tends to produce poorer material recovery than would be expected based upon the crude weights and purity (as assessed by ^{1}H NMR). Given the promising preliminary biological activities, it was of great interest to develop a method that would avoid time-consuming chromatographic separations yet still produce products with good purity, thereby enabling the rapid synthesis of sizable arrays by varying the aurone skeleton in both the benzofuranone and aldehyde-derived portions.

Avoiding chromatographic separation is not a new challenge for synthesis, and much effort has been directed to this end [22]. In some areas, particularly peptide, peptoid, and carbohydrate synthesis, supported synthesis has been a highly satisfactory solution [23]. Other options have given rise to the development of "click" chemistry, in which the reaction itself is sufficiently efficient to avoid the need for purification [24]. Additionally, there has been great attention given to the use of methods that can involve simple extraction for purification, particularly via the use of special tags, such as fluorous tags [25]. These tags serve to allow the desired products to be extracted into fluorous solvents, while the undesired by-products are left in the non-fluorous phase. Unfortunately, in the case of the condensation reaction to form aurones, there is no convenient and ubiquitous chemical handle by which to link either the benzofuranone or the aldehyde to a solid support. In addition to supported synthesis, another common option is to employ a supported scavenger to remove the unreacted reagents [26]. This appeared to be a much better option for aurone synthesis, as aldehyde scavenging is known and it would certainly be expected that aldehydes would react more rapidly with a scavenger than the enone-type functionality

present in the produced aurones. In addition, we had previously noted that the use of an excess of aldehyde under typical condensation reaction conditions, at the end, generates a mixture of only the desired aurone, unreacted aldehyde, and water, as the condensation reaction is quite efficient. Thus, if the excess aldehyde could be used and then readily removed, the desired aurone should be left with sufficient purity for direct use in biological assays without further purification. It is worth noting that a related approach has been reported by Brindle using bisulfate ion for the removal of aldehydes [27]. In this study, a large excess of sodium bisulfite in water was used to separate aldehydes from other less reactive compounds via simple extraction. The separation is generally efficient, but is quite sensitive to the water-miscible solvent employed and works best when a fairly non-polar solvent (25% ethyl acetate in hexanes in most cases) is used for the organic phase. Still, it is quick and exhibits good functional group compatibility.

2. Materials and Methods

General procedure for the condensation of benzofuranones followed by purification with polystyrene supported scavengers:

Benzofuranone (0.2 mmol) and aldehyde (0.4 mmol) were combined in a dry vial, then 0.7 g of neutral alumina was added, followed by 3 mL of dichloromethane. The reaction mixture was stirred for 12 h at 25 °C. After 12 h, a polymer-supported scavenger (2 equivalents of the scavenger with respect to the benzofuranone) was added to the reaction mixture and stirred for an additional 12 h. The reaction mixture was then filtered and washed with a 1:1:1 mixture of methanol, ethyl acetate, and acetone. The filtrate was then concentrated to dryness in vacuo to produce the desired aurone.

General procedure for the condensation of benzofuranones, followed by purification using isoniazid:

Benzofuranone (0.2 mmol) and aldehyde (0.4 mmol) were combined in a dry vial, then 0.7 g of neutral alumina was added, followed by 3 mL of dichloromethane. The reaction mixture was stirred for 12 h at 25 °C. After 12 h, isoniazid (0.4 mmol) was added to the reaction mixture and stirred for an additional 12 h. The reaction mixture was then filtered and washed with a 1:1:1 mixture of methanol, ethyl acetate, and acetone. The filtrate was then concentrated to dryness in vacuo and resuspended in ethyl acetate, followed by a 3x liquid–liquid extraction with 1 N HCl. The organic layer was then concentrated to dryness in vacuo to produce the desired aurone. All but one of these aurone products have been reported before in the literature and all exhibited satisfactory spectral data [18,20,21,28–30].

General method used for the analysis of the reaction kinetics of isoniazid with carbonyls:

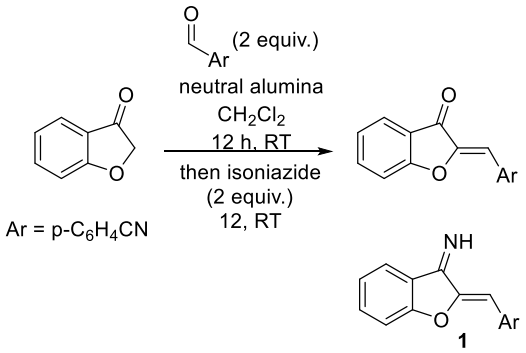
To a 2 mL autosampler vial was added 1 mL of a 0.05 M carbonyl solution containing a known concentration of the standard as indicated in the Supplementary Materials. A small stirring bar was then added, and the vial was sealed. The sample was then analyzed across 10 injections (11 for aldehydes) with a certain number of seconds between injections, as indicated in the Supplementary Materials. All runs were isothermal. Ten molar equivalents of isoniazid and 10 molar equivalents of neutral alumina were added to the reaction mixture approximately 120 s after the first injection. The reaction mixture was stirred at 600 rpm in between injections. The specific GC conditions for each substrate can be found in the Supplementary Materials.

3. Results and Discussion

Armed with this information, representative known and commercially available supported scavengers were explored. The reported scavengers have typically been nucleophilic amine- or hydrazine-based functional groups attached to a polystyrene support [31]. Three of these were surveyed for their use in a representative aurone-forming reaction, featuring sulfonylhydrazide, sulfonamide, and amine functionality for aldehyde scavenging (Table 1). In this reaction, benzofuranone was allowed to react with 2 equivalents of 4-cyanobenzaldehyde in neutral alumina and dichloromethane. After 24 h, the reaction mixture was filtered to remove the neutral alumina, and 2 equivalents of scavenger was

added, and the mixture was allowed to react for a further 24 h. The reaction was then filtered and dried to yield the product. Two of these three produced the desired aurone with high purity and reasonable yield after addition of the resin, stirring overnight, and then removal of the resin via filtration. Interestingly, the other resin (p-toluene sulfonyl hydrazide, polymer bound) failed to produce any of the desired aurone, but instead produced a material believed to be the corresponding imine **1**. The mechanism and source of this side reaction were not clear and are under further study, but it was cleanly reproducible, even with different batches of the hydrazide.

Table 1. Scavenging studies using different scavengers.



Entry	Scavenger [a]	Amount	% Yield	% Purity [b]	Cost [c]
1	p-Toluenesulfonyl hydroazide–polymer bound	200 mg	0 [d]	N/A	$18
2	Sulfonylamide–polymer bound	275 mg	72	>95	$43
3	Ethylenediamine-polymer bound	100 mg	72	>95	$12
4	isoniazid	55 mg	70	>95	$0.22

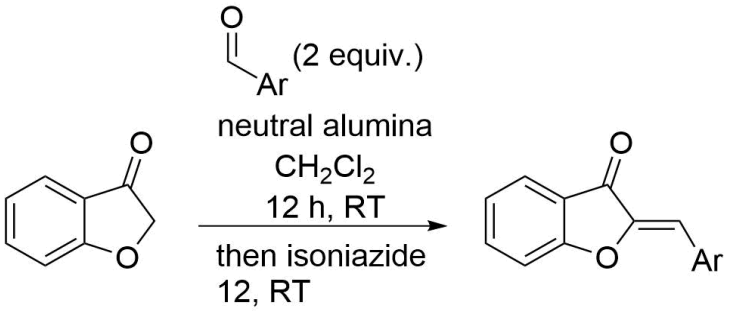
(a) In each case, 0.4 mmol of the scavenger was used, with all polymer-supported reagents being attached to cross-linked polystyrene and used as obtained from Aldrich. (b) Purity determined by ^{1}H NMR. (c) Prices from the Aldrich website. (d) The reaction afforded 20% of imine **1**.

While successful, these polymer-supported resins were not inexpensive and required significant excesses in order to obtain the consistent purity of the final products. What we desired was an equally effective scavenger that would be more cost-effective and perhaps require less of the scavenger. Recognizing that much of the weight in a polymer-supported scavenger is in the polymer portion, and also that imperfect swelling is often responsible for the need to use large molar excesses of the scavenger, it appeared that an easily separable, soluble, small-molecule scavenger would offer certain advantages. Interestingly, Olivera recently reported the use of isonicotinic acid hydrazide (isoniazid) loaded on an Amberlyst resin as a scavenger for aldehydes and ketones [32]. While very little was explored in this study beyond the ability of this resin-loaded scavenger to remove a few simple aldehydes and ketones from the solution, it appeared to be a highly promising option. At the same time, loading this scavenger on a resin (support) appeared to be unnecessary, as the loading relied on acid/base chemistry rather than covalent bonding. As a result, it was presumed that the isoniazid itself could be used as a soluble scavenger and then removed after condensation with the excess aldehyde by simple acid/base chemistry using a dilute aqueous hydrochloric acid wash to remove the isoniazid/aldehyde adduct. Thus, following the condensation reaction, isoniazid was added and the mixture was stirred overnight. Extraction with dilute hydrochloric acid was sufficient to remove the isoniazid and the scavenged aldehyde and leave the precipitated aurone with high purity and a similar yield to that obtained with the polymer-supported scavengers. (Table 1, Entry 4) It is important to note that this high yield, as well as control reactions between isoniazid and the aurone product, demonstrated excellent selectivity for the reaction with aldehydes and not the

aurone product, even with the prolonged reaction times employed for the scavenging stage of this sequence.

Based upon this initial success, several aldehydes were subjected to the same reaction and scavenging conditions in order to determine the influence of the electronic and steric factors of the aldehyde on the scavenging step. As can be seen from Table 2, in all but one case, the aurones were obtained with >95% purity as assessed by ^{1}H NMR. Isolated yields were more variable, but were all acceptable for the small scale (0.2 mmol) at which these reactions were performed and provided ample material for multiple biological screening campaigns.

Table 2. Variations in aldehyde using isoniazid as the scavenger.



Entry	Ar	% Yield	% Purity [a]
1	4-Cyanophenyl	70	>95
2	4-Trifluoromethylphenyl	44	>95
3	4-Dimethylaminophenyl	25	>95
4	4-Methylphenyl	57	>95
5	4-Methoxyphenyl	61	>95
6	4-Methyl carboxyphenyl	49	77
7	2-Bromophenyl	64	>95
8	3-Bromophenyl	39	>95
9	4-Bromophenyl	53	>95
10	2-Thiophenyl	36	>95
11	2-Furyl	37	>95

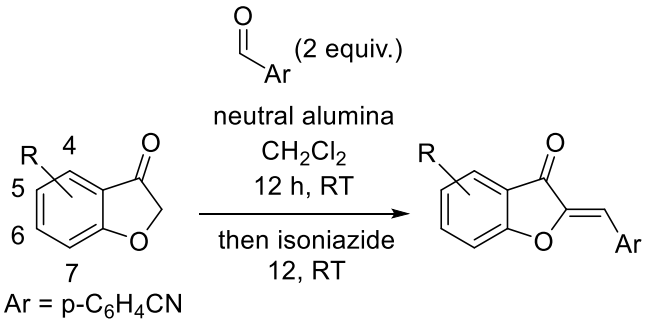
(a) Determined by ^{1}H NMR.

Although the benzofuranone was not expected to have any particular influence on the scavenging, a smaller series of modifications of that portion was also explored (Table 3). Since we were most interested in aurone compounds that did not feature the usual oxygenation found in natural aurones, and since we were interested in aurones which might undergo further diversification chemistry, we elected to study some halogenated benzofuranones. While most of these reactions were also quite successful, this study served to highlight one important consideration in the application of scavenging synthesis to aurones. The initial yields were rather disappointing and variable until it was noted that many of the products had very poor solubility in methylene chloride. Eventually, all the final filtrations were performed with an equal-volume mixture of methanol, ethyl acetate, and acetone. This solution was concentrated, resuspended in ethyl acetate, extracted with 1 N HCl, dried, and then concentrated. This modified procedure resulted in improved and reproducible recovery for all substrates and served to illustrate that recovery by this approach is dependent upon good solubility in the reaction solvent so that the product does not remain trapped on the neutral alumina.

While successful for aurones, this method has great potential for a wide range of carbonyl-based reactions, assuming that reasonable selectivity for scavenging can be realized. To explore the rate of the reaction and the potential selectivity, a series of carbonyl compounds were treated with isoniazid and neutral alumina in methylene chloride, and the rate of the reaction was followed by GC/MS (Table 4). Several interesting observations were made in the course of this effort. First, attempts to scavenge aldehydes in methylene

chloride in the presence of isoniazid without neutral alumina resulted in very slow reaction rates. Using more polar solvents (DMF, DMSO, and even methanol) resulted in much more rapid reactions, as is typical for reactions forming hydrazones, oximes, and the related carbonyl derivatives [33]. Including the neutral alumina, though, was sufficient to promote the scavenging reaction. As a result, all scavenging reactions were performed in methylene chloride in the presence of neutral alumina and 10 molar equivalents of isoniazid. As can be seen in Table 4, aldehydes generally reacted fairly rapidly, including one example each of an aliphatic and alkenyl aldehyde. Aliphatic ketones reacted at a comparable rate, but aromatic ketones (acetophenone and benzophenone) were much slower. Interestingly, a β-ketoester reacted quite rapidly but, not surprisingly, simple esters did not react to any appreciable extent. As a result, there appears to be considerable potential for the use of isoniazid as an aldehyde and even as an aliphatic ketone scavenger. It is also worth noting that these reaction rates indicate that the length of time for the scavenging step can be greatly reduced from 12 h and still result in complete removal of the excess aldehyde.

Table 3. Variations in benzofuranone using isoniazid as the scavenger.



Entry	Substituent	% Yield	% Purity [a]
1	4-Chloro	46	>95
2	5-Chloro	31	>95
3	4-Fluoro	55	>95
4	6-Fluoro	39	>95
5	5-Bromo	68	>95

(a) Determined by ^{1}H NMR.

Table 4. Carbonyl's reactivity with isoniazid.

Carbonyl Compound	Mean Rate Constant (10^3 s^{-1})	Relative Rate
Benzaldehyde	−0.410 ± 0.047	1.00
4-Nitrobenzaldehyde	−2.350 ± 0.500	5.73
4-Cyanobenzaldehyde	−1.399 ± 0.271	3.41
4-Bromobenzaldehyde	−0.584 ± 0.088	1.42
4-Methylbenzaldehyde	−0.141 ± 0.024	0.34
4-Methoxybenzaldehyde	−0.468 ± 0.054	1.14
3-Methoxybenzladehyde	−0.731 ± 0.053	1.78
2-Methoxybenzaldehyde	−2.583 ± 0.629	6.30
Trans-cinnamaldehyde	−0.844 ± 0.084	2.06
Dihydrocinnamaldehyde	−1.509 ± 0.620	3.68
Thiophene-2-carboxyaldehyde	−0.320 ± 0.072	0.78
Furan-2-carboxaldehyde	−1.433 ± 0.364	3.50
2-Octanone	−0.0436 ± 0.00548	0.11
Cyclohexanone	−0.846 ± 0.0180	2.06
Acetophenone	0.00045 ± 0.0028	0.00
Benzophenone	−0.0047 ± 0.0024	0.01
Ethyl acetoacetate	−0.150 ± 0.0102	0.37
Butyl acetate	−0.0013 ± 0.0025	0.00
Methyl benzoate	−0.00024 ± 0.0014	0.00

4. Conclusions

In conclusion, this scavenging synthesis has greatly increased our ability to synthesize new aurone analogs in a timely manner. Now, the preparation of new collections of larger numbers of compounds can be realistically accomplished in a matter of a few hours' effort over 2 days, rather than the much greater effort that was required using conventional purification. It is fully expected that this same scavenging approach can be applied to many other reactions of the highly versatile aldehyde functional group, thereby enabling convenient and rapid access to the arrays generated by these reactions as well. The application of this method to further aurone analog arrays and the biological testing of these compounds is underway, as is the extension of this scavenging approach to other reactions involving aldehydes.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/org4010004/s1. Detailed procedures, full spectral analysis, data, and calculations for the reaction rates as well as the GC and sampling conditions.

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

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

References

1. Bate-Smith, E.C.; Geissman, T.A. Benzalcoumaranones. *Nature* **1951**, *167*, 688. [CrossRef]
2. Mazziotti, I.; Petrarolo, G.; La Motta, C. Aurones: A Golden Resource for Active Compounds. *Molecules* **2022**, *27*, 2. [CrossRef] [PubMed]
3. Sui, G.; Li, T.; Zhang, B.; Wang, R.; Hao, H.; Zhou, W. Recent advances on synthesis and biological qactivities of aurones. *Bioorg. Med. Chem.* **2021**, *29*, 115895. [CrossRef]
4. Sutton, C.L.; Taylor, Z.E.; Farone, M.B.; Handy, S.T. Antifungal activity of substituted aurones. *Bioorg. Med. Chem. Lett.* **2017**, *27*, 901. [CrossRef] [PubMed]
5. Park, H.S.; Nelson, D.E.; Taylor, Z.E.; Hayes, J.B.; Cunningham, K.D.; Arivett, B.A.; Ghosh, R.; Wolf, L.C.; Taylor, K.M.; Farone, M.B.; et al. Suppression of LPS-induced NF-κB activity in macrophages by the synthetic aurone, (Z)-2-((5-(hydroxymethyl) furan-2-yl) methylene) benzofuran-3(2H)-one. *Int. Immunopharm.* **2017**, *43*, 116. [CrossRef]
6. Schmitt, J.; Handy, S.T. A golden opportunity: Benzofuranone modifications of aurones and their influence on optical properties, toxicity, and potential as dyes. *Beilstein J. Org. Chem.* **2019**, *15*, 1781–1785. [CrossRef] [PubMed]
7. Algahtani, F.M.; Arivett, B.A.; Taylor, Z.E.; Handy, S.T.; Farone, A.L.; Farone, M.B. Chemogenomic profiling to understand the antifungal action of a bioactive aurone compound. *PLoS ONE* **2019**, *14*, e0226068.
8. Alqahtani, F.M.; Handy, S.T.; Sutton, C.L.; Farone, M.B. Combining Genome-Wide Gene Expression Analysis (RNA-seq) and a Gene Editing Platform (CRISPR-Cas9) to Uncover the Selectively Pro-oxidant Activity of Aurone Compounds Against *Candida albicans*. *Front. Microbiol.* **2021**, *12*, 708267. [CrossRef]
9. Iwashina, T. The structure and distribution of the flavonoids in plants. *J. Plant Res.* **2000**, *113*, 287. [CrossRef]
10. Agrawal, N.N.; Soni, P.A. A New Process for the Synthesis of Aurones by Using Mercury (II) Acetate in Pyridine and Cupric Bromide in Dimethyl Sulfoxide. *Indian J. Chem.* **2006**, *45*, 1301–1303. [CrossRef]
11. Thanigaimalai, P.; Yang, H.M. Structural requirement of chalcones for the inhibitory activity of interleukin-5. *Bioorg. Med. Chem.* **2010**, *18*, 4441–4445. [CrossRef] [PubMed]
12. Taylor, C.; Bolshan, Y. Metal-Free Synthesis of Ynones from Acyl Chlorides and Potassium Alkynyltrifluoroborate Salts. *Tetrahedron Lett.* **2015**, *56*, 4392–4396. [CrossRef]
13. Harkat, H.; Blanc, A.; Weibel, J.-M.; Pale, P. Versatile and expeditious synthesis of aurones via Au I-catalyzed cyclization. *J. Org. Chem.* **2008**, *73*, 1620–1623. [CrossRef] [PubMed]

14. Liu, J.M.; Liu, M.W.; Yue, Y.Y.; Zhang, N.F.; Zhang, Y.I.; Zhuo, K.I. Construction of the flavones and aurones through regioselective carbonylative annulation of 2-bromophenols and terminal alkynes. *Tetrahedron Lett.* **2013**, *54*, 1802–1807. [CrossRef]
15. Qi, X.X.; Li, R.; Wu, X.F. Selective Palladium-catalyzed carbonylative synthesis of aurones with formic acid as the CO source. *RSC Adv.* **2016**, *6*, 2810–62813. [CrossRef]
16. Kayal, S.; Mukherjee, S. Catalytic enantioselective cascade Michael/cyclization reaction of 3-isothiocyanato oxindoles with exocyclic α,β-unsaturated ketones en route to 3,2′-pyrrolidinyl bispirooxindoles. *Org. Biomol. Chem.* **2016**, *14*, 10175–10179. [CrossRef]
17. Lee, Y.H.; Shin, M.C.; Yun, Y.D.; Shin, S.Y.; Kim, J.M.; Seo, J.M.; Kim, N.-J.; Ryu, J.H.; Lee, Y.S. Synthesis of aminoalkyl-substituted aurone derivatives as acetylcholinesterase inhibitors. *Bioorg. Med. Chem.* **2015**, *23*, 231–240. [CrossRef]
18. Varma, R.S.; Varma, M. Alumina-mediated condensation. A simple synthesis of aurones. *Tetrahedron Lett.* **1992**, *33*, 5937. [CrossRef]
19. Villemin, D.; Martin, B.; Bar, N. Application of Microwave in Organic Synthesis. Dry Synthesis of 2-Arylmethylene-3(2)-naphthofuranones. *Molecules* **1998**, *3*, 88. [CrossRef]
20. Venkateswarlu, S.; Murty, G.N.; Saryanarayana, M. "On water" synthesis of aurones: First synthesis of 4,5,3′,4′,5′-pentamethoxy-6-hydroxyaurone from *Smilax riparia*. *ARKIVOC* **2017**, *4*, 303. [CrossRef]
21. Hawkins, I.; Handy, S.T. Synthesis of aurones under neutral conditions using a deep eutectic solvent. *Tetrahedron* **2013**, *69*, 9200. [CrossRef]
22. Yellol, G.S.; Sun, C.-M. *Green Techniques for Organic Synthesis and Medicinal Chemistry*; Zhang, W., Cue, B.W., Jr., Eds.; John Wiley and Sons: Hoboken, NJ, USA, 2012; pp. 393–442.
23. Lu, J.; Toy, P.H. Organic polymer supports for synthesis and for reagent and catalyst immobilization. *Chem. Rev.* **2009**, *109*, 815–836. [CrossRef] [PubMed]
24. Moses, J.E.; Moorhouse, A.D. The growing applications of click chemistry. *Chem. Soc. Rev.* **2007**, *36*, 1249–1262. [CrossRef] [PubMed]
25. Le Lamer, A.-C.; Gouault, N.; David, M.; Boustie, J.; Uriac, P. Method for the parallel synthesis of alpha-methylene-gamma-lactones from a fluorous acrylate. *J. Comb. Chem.* **2006**, *8*, 643–645. [CrossRef]
26. Ley, S.V.; Baxendale, I.R.; Bream, R.N.; Jackson, P.S.; Leach, A.G.; Longbottom, D.A.; Nesi, M.; Scott, J.S.; Storer, R.I.; Taylor, S.J. Multi-step organic synthesis using solid-supported reagents and scavengers: A new paradigm in chemical library generation. *J. Chem. Soc. Perkin Trans. 1* **2000**, *23*, 3815. [CrossRef]
27. Boucher, M.M.; Furigay, M.H.; Quach, P.K.; Brindle, C.S. Liquid–Liquid Extraction Protocol for the Removal of Aldehydes and Highly Reactive Ketones from Mixtures. *Org. Process Res. Dev.* **2017**, *21*, 1394–1403. [CrossRef]
28. Kafle, A.; Bhatarai, S.; Handy, S.T. An Unusual Triazole Synthesis from Aurones. *Synthesis* **2020**, 2337–2346.
29. Taylor, K.M.; Taylor, Z.E.; Handy, S.T. Rapid synthesis of aurones under mild conditions using a combination of microwaves and deep eutectic solvents. *Tetrahedron Lett.* **2017**, *58*, 240–241. [CrossRef]
30. Xu, H.; Ziao, H.; Hu, X.; Zuan, G.; Li, P.; Zhang, Z. Synthesis of Fully Substituted 5-(o-Hydroxybenzoyl)imidazoles via Iodine-Promoted Domino Reactions of Aurones with Amidines. *J. Org. Chem.* **2022**, *87*, 16204–16212. [CrossRef]
31. Flynn, D.L.; Crich, J.Z.; Devraj, R.V.; Hockerman, S.L.; Parlow, J.J.; South, M.S.; Woodard, S. Chemical Library Purification Strategies Based on Principles of Complementary Molecular Reactivity and Molecular Recognition. *J. Am. Chem. Soc.* **1997**, *119*, 4874. [CrossRef]
32. De Oliveira, A.V.B.; Kartnaller, V.; Pedrosa, M.S.P.; Cajaiba, J.J. Isoniazid as an Aldehdye Scavenger: Analysis of Its Kinetics, Selectivity, and Practicality in Purifying Organic Reactions. *Appl. Polym. Sci.* **2015**, *132*, 1.
33. Kassehin, U.C.; Gbaguidi, F.A.; Kapanda, C.N.; McCurdy, C.R.; Poupaert, J.H. Solvent effect and catalysis in the synthesis of thiosemicarbazone derivatives from ketones and 4′-phenylthiosemicarbazide. *Afr. J. Pure App. Chem.* **2014**, *8*, 110–115.