molbank

MDPI

Short Note

1-(3,4-Dimethoxyphenyl)-3-(4-methoxyphenyl)-3-(1*H*-1,2,4-triazol-1-yl)propan-1-one

Anna Nacher-Luis and Isidro M. Pastor *

Organic Chemistry Department and Institute of Organic Synthesis (ISO), University of Alicante, Crta. San Vicente del Raspeig s/n, 03690 San Vicente del Raspeig, Alicante, Spain; anna.nacher@ua.es
* Correspondence: ipastor@ua.es; Tel.: +34-965903728

Abstract: The study of new catalytic protocols for the synthesis of organic compounds with a more sustainable perspective is of interest. The use of ionic organic solids, such as 1,3-bis(carboxymethyl) imidazolium chloride as a catalyst has allowed the Michael addition of N-heterocycles to chalcones. This methodology has been applied to the unique preparation of the potential bioactive compound 1-(3,4-dimethoxyphenyl)-3-(4-methoxyphenyl)-3-(1*H*-1,2,4-triazol-1-yl)propan-1-one with moderate yield, due to the retro-Michael reaction. Both synthetic reactions (i.e., preparation of chalcone and triazole Michael-addition to chalcone) have good green metrics.

Keywords: N-heterocycle; chalcone; 1,4-addition; catalysis; organic synthesis

1. Introduction

Nitrogen-containing heteroarene units are usually present in natural products and biologically active synthetic compounds [1,2], being important as bioactive compounds due to their stability and ability to bind "privileged structures" through hydrogen-bonding [3]. Triazole derivatives produce a variety of biological effects [4,5], due to their structural characteristics that make it easier to bind with target molecules. Among them, β-azolyl ketones constitute a family of compounds of potential interest [6]. Thus, 3-aryl-3-triazolylpropiophenones have been described as efficient components in fungicide, bactericide, and herbicide formulations [7,8].

The synthesis of β-heteroarylated carbonyl compounds is of interest, and it can be achieved through (a) reaction between ketones, formaldehyde and N-heterocycles [9], (b) nucleophilic substitution of β-chloro or β-(dialkylammonium) ketones with nitrogen heterocycles [10,11], or (c) conjugate addition of N-heterocycles to α,β-unsaturated ketones [12–14]. Among them, the aza-Michael reaction constitutes a synthetic tool of great importance [15], being the best atom-efficient synthetic protocol. This type of transformation provides access to β-aminocarbonyl derivatives as valuable precursors of bioactive compounds. The aza-Michael reaction can be carried out in the absence of a catalyst for certain activated nucleophiles and alkenes. However, the use of catalysts has made it possible to extend the scope of the reaction. Thus, this type of addition has been achieved under both acidic and basic conditions, using organocatalysts, metal salts or transition metal complexes [15]. There are several protocols with a fair scope in the addition of nitrogen-centered nucleophiles to activated alkenes, although in the case of chalcones, only aromatic amines have been successfully added [16,17]. Thus, the addition of N-heterocyclic compounds to chalcones has a particular interest, being a less considered transformation. In addition, the intrinsic feature of the reaction being equilibrated through retro-Michael makes the study of this synthetic process of special interest [18].

Our research group has been developing catalytic processes that allow the synthesis of compounds in a more sustainable manner. Thus, we have been working on the

Citation: Nacher-Luis, A.; Pastor, I.M. 1-(3,4-Dimethoxyphenyl)-3-(4-methoxyphenyl)-3-(1*H*-1,2,4-triazol-1-yl)propan-1-one. *Molbank* **2024**, *2024*, M1791. https://doi.org/10.3390/M1791

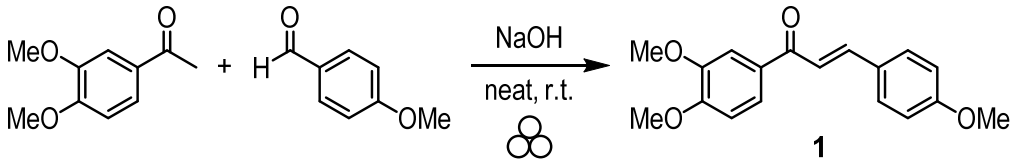
Academic Editor: Luke R. Odell

Received: 14 February 2024
Revised: 29 February 2024
Accepted: 8 March 2024
Published: 12 March 2024

use of ionic organic solids (IOS) as a catalyst in the absence of solvents in different synthetic transformations to prepare compounds of potential interest [19,20], such as allyl-substituted anilines, allyl-substituted N-heterocycles, quinolines, acridines, and thiophenes. Based on that, we have postulated the possibility of using an ionic organic solid (IOS), such as 1,3-bis(carboxymethyl)imidazolium chloride, as a catalyst to carry out an aza-Michael process between chalcones and N-heterocycles in the absence of solvents [21]. Preliminary studies have led to the preparation of the 1,3-diaryl-3-triazolylpropan-1-one described herein.

2. Results and Discussion

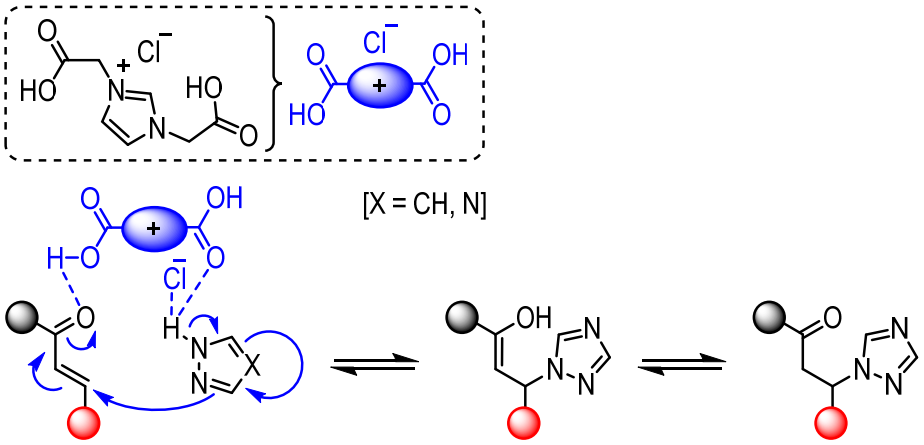
The preparation of chalcones can be straightforwardly achieved from an aromatic aldehyde and an acetophenone in the presence of a basic catalyst. To perform the process in a more sustainable way, we focused on carrying out the reaction in the absence of any solvent, considering montmorillonite [22] and sodium hydroxide [23] as catalysts. Based on previous studies, we selected NaOH due to the possibility of carrying out the process at room temperature with a much better outcome [21]. Thus, the 1-(3,4-dimethoxyphenyl)-3-(4-methoxyphenyl)prop-2-enone (**1**) was prepared by mixing 4-methoxybenzaldehyde and 3,4-(dimethoxy)phenyl methyl ketone in the presence of a catalytic amount of sodium hydroxide (Scheme 1), via a mechanochemical process. Moreover, the product was isolated through simple recrystallization in ethanol, avoiding purification for better environmental impact [24]. Indeed, the E-factor for the whole process is 8.4, being the main part of waste due to the solvent (ethanol) employed for recrystallization. It is worth noting that ethanol can be partially recovered producing a reduction of the E-factor to a value of 2.1. Moreover, this procedure has an atom economy (AE) value of 0.94 and a stoichiometric factor (SF) of **1** (see Supplementary Materials), since the reactants are employed in the proper stoichiometric ratio and there is only one equivalent of water as a byproduct.



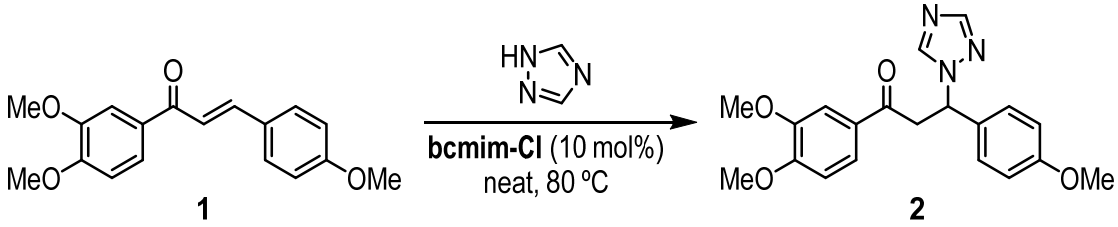
Scheme 1. Preparation of chalcone **1** by mechanochemical reaction.

Based on our experience employing 1,3-bis(carboxymethyl)imidazolium (**bcmim-Cl**) chloride as a catalyst in different transformations [19] since it enables the establishment of favorable interactions with the reagents facilitating the process in the absence of solvent, the study of this catalyst (**bcmim-Cl**) for the 1,4-addition of nitrogen-containing heterocycles to chalcones was proposed. As expected, a preliminary study performed in our laboratory showed that the reaction of chalcones with pyrazoles and triazoles as nucleophiles in the presence of catalyst **bcmim-Cl** under solvent-free conditions resulted in the formation of the corresponding 1,3-diaryl-3-(azol-1-yl)propan-1-one, although in moderately low yields [21]. A possible activation of the reagents by **bcmim-Cl** (Scheme 2) would approximate them to react in the absence of solvents. The proposed interactions are like those favoring the formation of eutectic mixtures [25–27].

Despite the moderate yields, the protocol has allowed the obtention of compounds of interest due to their potential bioactivity. The addition of 1,2,4-triazole to chalcone **1** resulted in the formation of a new compound **2**. Thus, the reaction was performed by heating both reagents in the presence of **bcmim-Cl** (10 mol%) at 80 °C (Scheme 3), observing after the completion of the reaction that triazole was partially sublimated causing the reaction not to give better yields. The use of a larger amount of triazole or the modification of reaction time and temperature did not lead to better results, and since the retro-Michael reaction restores the starting reagents [18], it was considered that this equilibrium does not allow better results to be obtained under the conditions studied (Scheme 2).



Scheme 2. Possible activation of reactants by **bcmim-Cl**, and equilibrium between Michael-adduct and reactants.



Scheme 3. Preparation of compound **2** mediated by **bcmim-Cl**.

The ^{1}H-NMR and ^{13}C-NMR analyses were recorded using deuterated chloroform showing evidence of the corresponding product **2** (see Supplementary Materials). In the ^{1}H-NMR spectra, apart from the three singlets (3.79, 3.91, and 3,94 ppm) corresponding to the methoxy groups and the signals of the aromatic protons in the phenyl substituents, there are signals that clearly confirm the presence of the product. Thus, two broad singlets at 7.92 and 8.18 relate to the triazole-ring protons, three signals of double doublet correspond to diastereotopic protons α to the carbonyl (3.61 and 4.33 ppm), and proton β to carbonyl (6.14 ppm). The ^{13}C-NMR spectra display signals for the 18 different carbons in the molecule. The signal of the carbonyl carbon (194.4) is a typical value for an aromatic ketone without a conjugated double bond.

Green metrics were calculated for the reaction depicted in Scheme 3 to evaluate the impact of this methodology (see Supplementary Materials). The protocol has perfect values of atom economy (AE = 1) and stoichiometric factor (SF = 1). Despite the moderate yield (38%), due to the retro-Michael, the E-factor considering the material recovered is 10.3. Thus, the total E-factor is 53.3 but the catalyst and part of the recrystallization solvent can be recovered, reducing the impact of the synthetic procedure.

3. Materials and Methods

All commercially available reagents were purchased (Acros, Aldrich, Fluka) and used without further purification. Melting points were determined using a Gallenkamp capillary melting point apparatus (model MPD 350 BM 2.5) and are uncorrected. ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded at the Research Technical Services of the University of Alicante (SSTTI-UA; https://sstti.ua.es/en; accessed on 11 March 2024), employing a Bruker AC-300. Chemical shifts (δ) are given in ppm and the coupling constants (*J*) in Hz. Deuterated chloroform ($CDCl_3$) was used as the solvent, and tetramethylsilane (TMS) was used as the internal standard. Low-resolution mass spectra (LRMS) with electronic ionization (EI) were obtained with an Agilent GC/MS-5973 Network spectrometer provided with an EI source (70 eV) and helium as mobile phase. Samples were introduced through injection through a gas chromatograph Hewlett-Packard HP-6890,

equipped with a Hp-5MS column (30 m length, 0.25 mm internal diameter, and 0.25 µm film thickness: crosslinking 5% PH ME siloxane). Detected fragmentations are given as *m*/*z* with relative intensities in parenthesis (%). The conversion of the reactions and purity of the products were determined through gas chromatography (GC) analysis employing a Younglin 6100GC equipped with a flame ionization detector and a Phenomenex ZB-5MS column (30 m length, 0.25 mm internal diameter, and 0.25 µm film thickness, crosslinking 5% PH ME siloxane) using nitrogen (2 mL/min) as the carrier gas and 270 °C in the injector block. The standard injection method was 60 °C as initial temperature (held for 3 min) and 15 °C/min until 270 °C (held for 10 min). Infrared (IR) spectra were recorded with an FT-IR 4100 LE (JASCO, Pike Miracle ATR) spectrometer. Spectra were recorded from neat samples and wavenumbers (ν) are given in cm^{-1}.

Catalyst **bcmim-Cl** was prepared as previously described by our group, [19]. 1,3-Bis(carboxymethyl)imidazolium chloride: white solid; ^{1}H-NMR (400 MHz, D_2O) δ_H = 8.84 (def. t, *J* = 1.6 Hz, 1H, NCHN), 7.47 (d, *J* = 1.6 Hz, 2H, CHCH), 4.87 (s, 4H, 2×CH_2) ppm; ^{13}C-NMR (101 MHz, D_2O) δ_C = 169.7, 138.1, 123.4, 50.1 ppm.

1-(3,4-Dimethoxyphenyl)-3-(4-methoxyphenyl)prop-2-enone (**1**). A mixture of 4-methoxybenzaldehyde (2 mmol, 272 mg), 3,4-dimethoxyacetophenone (2 mmol, 360 mg) and NaOH (40 mg) were ground in a mortar and pestle for 10 min. The product was recrystallized with ethanol, giving a yellowish solid (83% yield). M.p. = 85–86 °C (EtOH; lit. [28] 86–87 °C); ^{1}H-NMR (300 MHz, $CDCl_3$) δ_H = 7.81 (d, *J* = 15.6 Hz, 1H, ArCH), 7.71–7.60 (m, 4H, ArH), 7.45 (d, *J* = 15.6 Hz, 1H, COCH), 6.97–6.93 (m, 3H, ArH), 3.99 (s, 3H, CH_3), 3.98 (s, 3H, CH_3), 3.87 (s, 3H, CH_3) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$) δ_C = 188.6 (C=O), 161.5 (ArC-OMe), 153.1 (ArC-OMe), 149.2 (ArC-OMe), 143.8 (*C*H=CHCO), 131.6 (ArC), 130.1 (2C, ArCH), 127.8 (ArC), 122.8 (ArCH), 119.3 (*C*HCO), 114.4 (2C, ArCH), 110.8 (ArCH), 109.9 (ArCH), 56.1 (OCH_3), 56.0 (OCH_3), 55.4 (OCH_3) ppm; MS (EI, 60 eV) *m*/*z*: 299 [M^+ + 1] (23%), 298 [M^+] (100), 297 (24), 283 (35), 268 (12), 267 (53), 255 (11), 190 (12), 165 (25), 161 (23), 133 (13).

1-(3,4-Dimethoxyphenyl)-3-(4-methoxyphenyl)-3-(1*H*-1,2,4-trizaol-1-yl)propan-1-one (**2**). A mixture of chalcone **1** (0.5 mmol, 150 mg), 1*H*-1,2,4-triazole (0.5 mmol, 35 mg), and bcmim-Cl (0.05 mmol, 11 mg) was heated at 80 °C for 24 h. After reaction time, ethyl acetate (4 mL) was added and filtered through a pad of celite to remove the catalyst. The product was purified through recrystallization (EtOAc), giving a white solid (37% yield). M.p. = 174–175 °C); *ν* = 3116 (arC-H), 1666 (C=O), 1585, 1511, 1257 (arC-C), 1126, 1014, 817(arC-H)) cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ_H = 8,18 (s, 1H, ArH), 7.92 (s, 1H, ArH), 7.62 (dd, *J* = 8.3, 1.9 Hz, 1H, ArH), 7.47 (d, *J* = 1.9 Hz, 1H, ArH), 7.39–7.34 (m, 2H, ArH), 6.91–6.87 (m, 3H, ArH), 6.14 (dd, *J* = 8.5, 5.1 Hz, 1H, $COCH_2$), 4.33 (dd, *J* = 17.5, 8.5 Hz, 1H, $COCH_2$), 3.94 (s, 3H, CH_3), 3.91 (s, 3H, CH_3), 3.79 (s, 3H, CH_3), 3.61 (dd, *J* = 17.5, 5.1 Hz, 1H, ArCHN) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$) δ_C = 194.4 (C=O), 159.7 (ArC-OMe), 153.7 (ArC-OMe), 151.7 (NCN), 149.1 (ArC-OMe), 143.8 (NCN), 130.7 (ArC), 130.1 (ArC), 129.4 (ArCH), 128.3 (2C, ArCH), 122.9 (ArCH), 114.3 (2C, ArCH), 110.0 (ArCH), 58.8 (CH_2CH), 56.1 (OCH_3), 55.9 (OCH_3), 55.3 (OCH_3), 43.2 (CH_2) ppm; MS (EI, 60 eV) *m*/*z*: 368 [M^+ + 1] (11%), 367 [M^+] (44), 299 (22), 298 (100), 297 (23), 283 (3), 267 (47), 202 (67), 188 (21), 175 (25), 165 (63), 134 (38), 133 (97); elemental analysis: calcd. for $C_{20}H_{21}N_3O_4$, C 65.38, H 5.76, N 11.44%, found, C 64.90, H 5.90, N 11.16%.

4. Conclusions

To conclude, the efficiency of an ionic organic solid as a heterogeneous catalyst promotes the addition of N-heterocycles (such as 1*H*-1,2,4-triazole) to chalcones in the absence of any solvent or any additive. The protocol has been applied to the preparation of 1-(3,4-dimethoxyphenyl)-3-(4-methoxyphenyl)-3-(1*H*-1,2,4-triazol-1-yl)propan-1-one, being a compound with potential bioactivity since it is related t herbicide, fungicide, and bactericide products. The synthesis proposed contains the preparation of a chalcone by a methodology with good to excellent green metrics, and the subsequent conjugated addition of 1,2,4-triazole presents fair values of green metrics, despite the moderate yield.

Supplementary Materials: Figure S1: 1H-NMR spectrum of 1-(3,4-dimethoxyphenyl)-3-(4-methoxyphenyl)prop-2-enone; Figure S2: 13C-NMR spectrum of 1-(3,4-dimethoxyphenyl)-3-(4-methoxyphenyl)prop-2-enone; Figure S3: 1H-NMR spectrum of 1-(3,4-dimethoxyphenyl)-3-(1H-1,2,4-triazol-1-yl)propan-1-one; Figure S4: 13C-NMR spectrum of 1-(3,4-dimethoxyphenyl)-3-(1H-1,2,4-triazol-1-yl)propan-1-one.

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

Funding: This research was funded by Ministerio de Ciencia e Innovación (grant number PID2021-127332NB-I00), and the University of Alicante (grant numbers VIGROB-316, UASTI22-23, UADIF22-104).

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

Acknowledgments: The authors thank the administrative and technical support of the Research Technical Services of the University of Alicante (https://sstti.ua.es/en; accessed on 26 January 2024).

Conflicts of Interest: The authors declare no conflicts of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

References

1. Dewick, P.M. *Medicinal Natural Products: A Biosynthetic Approach*; John Wiley & Sons Ltd.: Chichester, UK, 2009.
2. Arora, P.; Arora, V.; Lamba, H.S.; Wadhwa, D. Importance of heterocyclic chemistry: A review. *Int. J. Pharm. Sci. Res.* **2012**, *3*, 2947–2954.
3. Heravi, M.M.; Zardsirjan, V. Prescribed drugs containing nitrogen heterocycles: An overview. *RSC Adv.* **2020**, *10*, 44247–44311. [CrossRef]
4. Zhang, H.-Z.; He, S.-C.; Peng, Y.-J.; Zhang, H.-J.; Gopala, L.; Tangadanchu, V.K.R.; Gan, L.-L.; Zhou, C.-H. Design, synthesis and antimicrobial evaluation of novel benzimidazole-incorporated sulfonamide analogues. *Eur. J. Med. Chem.* **2017**, *15*, 136165–136183. [CrossRef]
5. Min, Y.K.; Asami, T.; Fujioka, S.; Murofushi, N.; Yamaguchi, I.; Yoshida, S. New lead compounds for brassinosteroid biosynthesis inhibitors. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 425–430. [CrossRef]
6. Bhanuchandra, M.; Kuram, M.R.; Sahoo, A.K. A convenient approach to β-heteroarylated (C-N bond) ketones from Cs_2CO_3 promoted reaction between propargyl alcohols and nitrogen-heterocycles. *Org. Biomol. Chem.* **2012**, *10*, 3538–3555. [CrossRef]
7. Ehrhardt, H.; Mildenberger, H.; Sachse, B.; Hartz, P. Fungicide and Bactericide 3-aryl-3-oxo-propyl-1,2,4-Triazoles Derivatives. DE-Patent Number DE3020500A1, 21 January 1982.
8. Shephard, M.C.; Sugavanam, B.; Worthington, P.A.; Collins, D.J.; Griffin, D. Herbicidal Formulations. U.S. Patent Number US4113465, 12 September 1978.
9. Marrapu, V.K.; Mittal, M.; Shivahare, R.; Gupta, S.; Bhandari, K. Synthesis and evaluation of new furanyl and thiophenyl azoles as antileishmanial agents. *Eur. J. Med. Chem.* **2011**, *46*, 1694–1700. [CrossRef]
10. Kumar, L.; Sarswat, A.; Lal, N.; Jain, A.; Kumar, S.; Kumar, S.T.V.S.K.; Maikhuir, J.P.; Pandey, A.K.; Shukla, P.K.; Gupta, G. Design and synthesis of 3-(azol-1-yl)phenylpropanes as microbicidal spermicides for prophylactic contraception. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 176–181. [CrossRef]
11. Roman, G.; Comanita, E.; Comanita, B. Synthesis and reactivity of Mannich bases. Part 15: Synthesis of 3-(2-(1-pyrazolyl)ethyl)-1,2-benzisoxazoles. *Tetrahedron* **2002**, *58*, 1617–1622. [CrossRef]
12. Srivastava, N.; Banik, B.K. Bismuth nitrate-catalyzed versatile Michael reactions. *J. Org. Chem.* **2003**, *68*, 2109–2114. [CrossRef]
13. Lv, J.; Wu, H.; Wang, Y. Organocatalytic enantioselective aza-Michael additions of N-heterocycles to α,β-unsaturated enones. *Eur. J. Org. Chem.* **2010**, *2010*, 2073–2083. [CrossRef]
14. Bayindir, S.; Erdogan, E.; Kilic, H.; Saracoglu, N. An efficient synthesis of new aza-substituted indoles via Michael-type addition. *Synlett* **2010**, *10*, 1455–1458. [CrossRef]
15. Rulev, A.Y. Aza-Michael reaction: A decade later—Is the research over? *Eur. J. Org. Chem.* **2023**, *26*, e202300451. [CrossRef]
16. Ying, A.; Zhang, Q.; Li, H.; Shen, G.; Gong, W.; He, M. An environmentally bening protocol: Catalyst-free Michael addition of aromatic amines to α,β-unsaturated ketones in glycerol. *Res. Chem. Intermed.* **2013**, *39*, 517–525. [CrossRef]
17. Iida, H.; Tang, Z.; Yashiman, E. Synthesis and bifunctional asymmetric organocatalysis of helical poly(phenylacetylene)s bearing chinchona alkaloid pendants via a sulfonamide linkage. *J. Polymer Sci. A Polymer Chem.* **2013**, *51*, 2869–2879. [CrossRef]
18. Selvi, T.; Velmathi, S. Indium(III) triflate-catalyzed reactions of aza-Michael adducts of chalcones with aromatic amines: Retro-Michael addition versus quinoline formation. *J. Org. Chem.* **2018**, *83*, 4087–4091. [CrossRef]

19. Albert-Soriano, M.; Pastor, I.M. Anion-dependent imidazolium-based catalysts for allylation of aniline with tunable regioselectivity. *Adv. Synth. Catal.* **2020**, *362*, 2494–2502. [CrossRef]
20. Martos, M.; Pérez-Almarcha, Y.; Pastor, I.M. DES-type interactions to promote solvent-free and metal-free reactions between nitrogen-containing heterocycles and allylic alcohols. *Eur. J. Org. Chem.* **2022**, *2022*, e202201221. [CrossRef]
21. Nacher-Luis, A. *Estudio Sobre Sales de Imidazolio Para Aplicaciones en Síntesis Orgánica*; Degree Final Project; University of Alicante: Alicante, Spain, 2023; Available online: http://hdl.handle.net/10045/135324 (accessed on 28 February 2024).
22. Ballini, R.; Bosica, G.; Maggi, R.; Ricciutelli, M.; Righi, P.; Sartori, G.; Sartorio, R. Clay-catalysed solventless synthesis of *trans*-chalcones. *Green Chem.* **2001**, *3*, 178–180. [CrossRef]
23. Palleros, D.R. Solvent-free synthesis of chalcones. *J. Chem. Educ.* **2004**, *81*, 1345–1347. [CrossRef]
24. Andraos, J. *Reaction Green Metrics—Problems, Exercises, and Solution*; CRC Press (Taylor & Francis Group): Boca Raton, FL, USA, 2019.
25. Alonso, D.A.; Baeza, A.; Chinchilla, R.; Guillena, G.; Pastor, I.M.; Ramón, D.J. Deep eutectic solvents: The organic reaction medium of the century. *Eur. J. Org. Chem.* **2016**, *2016*, 612–632. [CrossRef]
26. Liu, Y.; Friesen, J.B.; McAlpine, J.B.; Lankin, D.C.; Chen, S.-N.; Pauli, G.F. Natural deep eutectic solvents: Properties, applications, and perspectives. *J. Nat. Prod.* **2018**, *81*, 679–690. [CrossRef] [PubMed]
27. Stephens, N.M.; Smith, E.A. Structure of deep eutectic solvents (DESs): What we know, what we want to know, and why we need to know it. *Langmuir* **2022**, *38*, 14017–14024. [CrossRef] [PubMed]
28. Pathak, V.; Ahmad, I.; Kahlon, A.K.; Hasanain, M.; Sharma, S.; Srivastava, K.K.; Sarkar, J.; Shankar, K.; Sharma, A.; Gupta, A. Syntheses of 2-methoxyestradiol and eugenol template based diarylpropenes as non-steroidal anticancer agents. *RSC Adv.* **2014**, *4*, 35171–35185. [CrossRef]