Synthesis of a Pyrrolo[1,2-\(a\)]quinazoline-1,5-dione Derivative by Mechanochemical Double Cyclocondensation Cascade

Vanessza Judit Kolcsár and György Szőllősi

1 Department of Organic Chemistry, Faculty of Science and Informatics, Institute of Chemistry, University of Szeged, Dóm tér 8, 6720 Szeged, Hungary
2 ELKH-SZTE, Stereochemistry Research Group, University of Szeged, Eötvös utca 6, 6720 Szeged, Hungary
* Correspondence: szollosi@chem.u-szeged.hu; Tel.: +36-62-544514

Abstract: N-heterocyclic compounds, such as quinazolinone derivatives, have significant biological activities. Nowadays, as the demand for environmentally benign, sustainable processes increases, the application of compounds from renewable sources, easily separable heterogeneous catalysts and efficient, alternative activation methods is of great importance. In this study, we have developed a convenient, green procedure for the preparation of 3a-methyl-2,3,3a,4-tetrahydropyrrolo[1,2-\(a\)]quinazoline-1,5-dione through a double cyclocondensation cascade using anthranilamide and ethyl levulinate. Screening of various heterogeneous Brønsted acid catalysts showed that Amberlyst® 15 is a convenient choice. By applying mechanochemical activation in the preparation of this N-heterotricyclic compound for the first time, it was possible to shorten the necessary time to three hours compared to the 24 h needed under conventional conditions to obtain a high yield of the target product.

Keywords: anthranilamide; ethyl levulinate; Amberlyst® 15; Brønsted acid; cascade reaction; mechanochemistry; quinazolinone; ball mill

1. Introduction

The pharmaceutical importance of N-heterocyclic compounds is indisputable [1]. Due to the biological activities of quinazolinone derivatives, such as anticancer, diuretic and antibacterial properties, these molecules caught the attention of organic chemists [2–8]. Among these, 2,3-dihydroquinazolin-4(1H)-ones are privileged building blocks in drug design, which are facilely prepared by the cyclocondensation of anthranilamides and aldehydes or ketones [2–4,9]. Various catalysts were used in these cyclocondensations, such as strong bases [10,11], strong mineral or weak organic Brønsted acids [10,12–16], sulfonic acids [4,10,17–21], Lewis acids [22–30] and ammonium salts [31,32].

Recent trends in the fine chemical industry require the development of sustainable, environmentally benign processes; thus, in the preparation of 2,3-dihydroquinazolin-4(1H)-ones, the application of catalyst- or solvent-free methods [33–36] and/or employing easily separable heterogeneous catalysts also became widely investigated [37–47]. Among the latter materials, surface-bonded sulfonic, sulfamic or sulfuric acids are privileged heterogeneous catalysts [48–56]. Methods replacing anthranilamide with compounds in situ transformed to 2-aminobenzamides, such as isatoic anhydride, 2-aminobenzonitrile, 2-nitro or 2-azidobenzamides, were also applied in cascade processes leading to 2,3-dihydroquinazolin-4(1H)-ones [13,57–63]. Besides their pharmaceutical use, 2,3-dihydroquinazolin-4(1H)-ones are easily transformed to quinazolinones by subsequent one-pot oxidation [11,19,20,64,65]. Moreover, the use of additionally functionalized carbonyl compounds allows the preparation of tricyclic hydroquinazoline derivatives through another consecutive one-pot cyclocondensation step [66–68]. Among the carbonyl compounds used in such cascade reactions, \(\gamma\)-keto carboxylic acids and esters were applied to obtain pyrrolo[1,2-\(a\)]quinazoline-1,5-dione derivatives [68–70]. As levulinic acid is a platform molecule obtained from biomass.
and its esterification can be activated by microwave in a solventless organocatalytic system [71–73], these allow the sustainable preparation of such N-heterotricyclic products using renewable resources.

On the other hand, advancements in the development of environmentally friendly methods were achieved by the application of alternative energy transmissions [74,75]. Among these, mechanochemical activation became widespread due to its operational simplicity and broad applicability [76–80]. Mechanochemical reactions performed in easily available mixer mills may be carried out in a solventless manner or using a minor amount of liquid for ensuring the proper energy transmission and mixing, termed liquid-assisted grinding (LAG). A wide range of milling conditions can be optimized to achieve high efficiency in various organic reactions, such as the agitation speed, the milling time and the size, number and material of the grinding media [81,82]. Finding appropriate conditions to efficiently carry out certain organic transformations by mechanochemical activation is still a challenging task and requires detailed studies. A variety of organic reactions were carried out by mechanochemical activation at a laboratory scale [76–85]. These studies indicated that, in most of these reactions, the time can be decreased significantly compared to conventional batch systems. Studies on mechanochemical reactions were also extended to cascade processes, resulting in the formation of valuable heterocyclic compounds [86–89].

Initial attempts to use mechanochemical activation in catalytic cyclocondensations leading to 2,3-dihydroquinazolin-4(1H)-ones were carried out in mortars by grinding the reaction components often followed by heating the mixtures [90–94]. Later, with the widespread application of ball mills in organic synthetic procedures, reactions of anthranilamide and aldehydes or ketones were also efficiently carried out in mixer mills, either solventless or in aqueous media and catalyst-free or catalyzed by potassium iodide or iodine [95,96]. However, the applicability of the mechanochemical activation in cascade double cyclocondensations of anthranilamide and bifunctional carbonyl compounds, to our knowledge, has not yet been explored.

Having in sight the increased importance of one-pot reactions [97], our present study aimed at developing an economic, green and sustainable process for the preparation of a tricyclic pyrrolo[1,2-a]quinazoline-1,5-dione derivative by two consecutive cyclocondensations occurring upon reacting anthranilamide and ethyl levulinate. For this, we attempted to use solid acids as heterogeneous catalysts and mechanochemical activation.

2. Results and Discussions

2.1. Catalytic Cascade Reaction of Anthranilamide and Ethyl Levulinate in the Batch System

The condensations of anthranilamide (1) and aldehydes or ketones occur through the formation of the corresponding Schiff base followed by a ring-closing step with the participation of the amide moiety (Scheme 1). Products with three condensed rings may be achieved under appropriate conditions with bifunctional carbonyl compounds, such as ethyl levulinate (2), as shown in Scheme 1. Thus, in the reaction of 1 and 2 the quinazolinone derivative 3 is formed which, via a second ring-closing step, provides the three-fused ring-containing product 4. Our initial goal was to choose an appropriate commercial heterogeneous catalyst which may ensure the formation of product 4 under convenient conditions. The study was carried out in a solventless manner in a batch system through magnetic stirring. To ensure proper mixing of the components, 1.5 equivalent (eq) 2 was applied. Measurements carried out without a catalyst showed that, at low temperature (60 °C), small conversion (Conv) of 1 could be achieved and that the second ring-closing step took place in a small ratio (see the selectivity of 4 (S4), Table 1, entry 1). However, the presence of the Schiff base was not detected at a significant amount, thus its formation rate may be the limiting step of 3 production. Increasing the reaction temperature (90 °C) had a positive effect on the conversion; however, production of 4 still resulted in a low yield (entry 2).
Scheme 1. The reaction of anthranilamide (1) and ethyl levulinate (2) resulting in the formation of 2,3-dihydroquinazolin-4(1H)-one (3) and pyrrolo[1,2-a]quinazoline-1,5-dione (4) derivatives.

Table 1. Effect of the catalyst in the reaction of 1 and 2.a.

| Entry | Catalyst          | Catalyst Amount | T (°C) b | t (h) c | Conv (%) d | S3 (%) e | S4 (%) e |
|-------|------------------|-----------------|----------|--------|------------|----------|----------|
| 1     | -                | -               | 60       | 24     | 40         | 83       | 15       |
| 2     | -                | -               | 90       | 24     | >99        | -        | 99 (90)  |
| 3     | Silica gel 60    | 125 mg          | 90       | 48     | 99         | 48       | 51       |
| 4     | Mont K10         | 125 mg          | 90       | 24     | >99        | 60       | 39       |
| 5     | Mont K10         | 125 mg          | 90       | 48     | >99        | 35       | 63       |
| 6     | Mont KSF         | 125 mg          | 90       | 48     | >99        | 40       | 58       |
| 7     | p-TsOH           | 5 mol%          | 60       | 24     | >99        | 48       | 51       |
| 8     | p-TsOH           | 5 mol%          | 90       | 24     | >99        | -        | 99 (90)  |
| 9     | Deloxan® ASP     | 100 mg          | 90       | 24     | >99        | 80 (70)  | 19       |
| 10    | Deloxan® ASP     | 125 mg          | 90       | 24     | >99        | -        | 98       |
| 11    | Nafion™ NR50     | 86 mg (2 pcs)   | 90       | 24     | >99        | 77 (61)  | 21       |
| 12    | Nafion™ NR50     | 84 mg (2 pcs)   | 90       | 24     | >99        | -        | 99 (88)  |
| 13    | Amberlyst® XN-1010 | 100 mg       | 60       | 24     | >99        | -        | 99 (90)  |
| 14    | Amberlyst® 15    | 100 mg          | 60       | 24     | >99        | -        | 99 (91)  |

a Reactions were carried out using 1 mmol 1 and 1.5 mmol 2 with magnetic stirring (600 rpm). b Reaction temperature. c Reaction time. d Conversion of 1 determined by gas chromatography (GC-FID). e Selectivities of products 3 and 4 were determined by GC-FID, the selectivities of other products were 1–3%. f In parentheses, the yield of the corresponding product following purification by flash chromatography (3) or by crystallization in ethyl acetate (4).

Next, we employed various commercial Brønsted acidic catalysts, which all provided high conversions after 24 or 48 h, some even at 60 °C. The selectivities highly depended on the properties of the applied catalyst. Silica gel and acid-treated montmorillonite clays (Mont K10, Mont KSF) (entries 3–6) were not able to provide high S4 selectivities. On the other hand, catalysts bearing sulfonic acid groups were active in catalyzing the formation of the aimed pyrrolo[1,2-a]quinazolinedione derivative (entries 7–14). The application of p-toluenesulfonic acid (p-TsOH) provided high S4 only under harsher reaction conditions (90 °C). The propylsulfonic polysiloxane resin (Deloxan® ASP) and the perfluorinated resin bearing sulfonic acid groups (Nafion™ NR50) were also efficient but, similarly to the p-TsOH, a higher temperature was necessary to obtain 4 (entries 9–12). The best results were provided by the polystyrene-based sulfonic acid-functionalized Amberlyst®-type catalysts (entries 13, 14), both of which afforded full conversions and close to exclusive formation of 4 at 60 °C. Based on these results, we choose to use Amberlyst® 15 in our further investigations.

Examination of the temperature effect was carried out both without a catalyst and with Amberlyst® 15 (see Supplementary Materials, Figure S1). In the absence of a catalyst, a temperature of 90 °C was necessary to achieve close to full conversion; however, S4 was low over the investigated temperature range, i.e., thermally the second ring-closing step occurred with a low rate. In contrast, by applying Amberlyst® 15, 1 was completely transformed...
and S4 increased by raising the temperature, approaching 100% at 60 °C. Thus, under the conditions used in this study, the second cyclization step required the use of an acid catalyst. The same conclusion may be drawn from results regarding the influence of the catalyst amount (Supplementary Materials, Figure S2). At 60 °C, at least 100 mg Amberlyst® 15 was necessary to obtain the desired product 4 in high proportion. Amberlyst® 15 is available from a commercial source in bead-like form. We have powdered it by pre-grinding the material in a ball mill for 10 min to increase its exposed surface sites (denoted as Amberlyst® 15P). By this method, the activity of the catalyst in the second cyclization could be increased significantly, reaching almost 30% higher selectivity of 4 compared to the reaction with the same amount (50 mg) of the commercial form (Figure S2).

Based on the results achieved with Amberlyst® 15P, we further optimized the reaction conditions using this material (Table 2). Decreasing the excess of the reactant to 1.1 eq resulted in lower 4 selectivity, suspected to be due to less efficient mixing of the slurry (Table 2, entries 1, 2). To improve the mixing of the components, the missing volume of 2 was replaced with methanol (MeOH). Close to full conversion and high S4 were obtained (entry 3). To further study the role of the catalyst, purified 3 (resulting from previous experiments) was used as the starting compound under identical conditions, both without (entry 4) and with Amberlyst® 15P (entry 5). In this case, the second ring-closing step did not occur unless the solid acid was present.

According to the above, the two cyclocondensation steps of this cascade reaction can be carried out neat, using as little as 1.1 eq 2 by applying a small amount of MeOH and pre-milled Amberlyst® 15 catalyst. The use of MeOH does not diminish the environmentally benign aspect of the method as it is among the organic solvents recommended for use even by some pharmaceutical companies [98]. Based on the obtained results so far and the known mechanism of the cyclocondensations [9,13,23,37,68,70], we could draw conclusions about the activation of the steps, as presented in Scheme 2. We observed that the first cyclization of the cascade reaction leading to 3 can be thermally promoted. Without using a catalyst at 60 °C, 40% conversion was obtained, which increased to 95% at a higher (90 °C) temperature. The product mixture mostly contained the intermediate product 3, but the formation of a small amount of 4 was also observed, which shows that heating may also promote the second step (Table 1, entries 1, 2). The effect of heating seemed negligible starting from 3 (Table 2, entry 4); however, by introducing Amberlyst® 15 into the system, intramolecular amide formation was accelerated (Table 2, entry 5). According to these findings, the first part of the reaction marked with blue arrows on Scheme 2 (steps a.–d.) can be promoted by heat as well as acid catalysts. Intramolecular amide formation, on the other hand, is mainly promoted by the acid catalyst (red arrows, steps e.–g.); thus, in our further studies, the use of a catalyst was necessary to obtain the target compound 4.

Table 2. Effect of 2 and methanol amount on the results obtained in the reaction of 1 and 2 a.

| Entry | EL Amount (eq) | MeOH Amount (µL) | Conv (%) b | S3 (%) c | S4 (%) c |
|-------|----------------|------------------|------------|----------|----------|
| 1     | 1.5            | -                | >99        | 35       | 64       |
| 2     | 1.1            | -                | >99        | 55       | 42       |
| 3     | 1.1            | 57               | >99        | 1        | 97 (89) f|
| 4 d,e | 1.1            | 57               | -          | 96       | 2        |
| 5 e   | 1.1            | 57               | -          | -        | 99 (91) f|

a Reactions were carried out using 50 mg pre-milled Amberlyst® 15P and 1 mmol 1 at 60 °C for 24 h. b Conversion by GC-FID. c Selectivities of 3 and 4 by GC-FID. d Reaction without catalyst. e Using 1 mmol 3 as the starting material (isolated by flash chromatographic purification of previously obtained reaction mixtures). f In parentheses, the yield of crystallized 4.
Scheme 2. The reaction mechanism of the cascade reaction: blue arrows are the catalytic steps which occurred thermally (a–d.) and the red arrows are steps requiring an acid catalyst (e–g.).

2.2. Mechanochemical Catalytic Cascade Reaction of Anthranilamide and Ethyl Levulinate

To make further steps towards the development of a sustainable method, we aimed to carry out the neat reaction of 1 and 2 in a ball mill. Based on the mechanochemical organic reactions recently reported in the literature [99,100], we started our experiments by applying grinding balls of different sizes (Table 3). The number of grinding beads was determined to have similar total volumes in each measurement.

Table 3. Effect of the size and number of grinding balls in the reaction of 1 and 2.

| Entry | Diameters of Balls (mm) | Number of Balls (pcs) | Conv (%)  | S3 (%)  | S4 (%)  |
|-------|-------------------------|-----------------------|-----------|---------|---------|
| 1     | 15                      | 1                     | 98        | 36      | 62      |
| 2     | 12                      | 1                     | 98        | 54      | 42      |
| 3     | 5                       | 25                    | 97        | 13      | 85      |
| 4     | 3                       | 125                   | >99       | 90 (80) | 94      |
| 5     | 5                       | 35                    | 98        | 4       | 94      |
| 6     | 5                       | 40                    | >99       | -       | 99 (92) |
| 7     | 5                       | 35                    | 77        | 78      | 20      |

*Reactions were carried out using 100 mg Amberlyst®, 15, 1 mmol 1 and 1.5 mmol 2 with an agitation speed of 30 Hz for 180 min. *Conversion by GC-FID. *Selectivities of 3 and 4 by GC-FID. *In parentheses, the yield of the purified 3 or 4. *90 min reaction.

Balls with a bigger diameter (Ø 15 and 12 mm) may provide high collision energy; however, only one piece fits into the jar without hindering another’s movement. Thus, only a low collision number can be achieved. Better 4 selectivity was observed using the Ø 15 mm ball (Table 3, entry 1) than applying the Ø 12 mm ball (entry 2), which shows the importance of collision energy in the second cyclization step. Using 25 pieces (pcs) of
Ø 5 mm grinding balls provided an even better result (entry 3). In this case, the higher collision number compensated for the decreased collision energy. However, the use of 125 pcs of Ø 3 mm beads was not efficient, probably due to their very low energy (entry 4). Based on these results, the use of Ø 5 mm balls was the best choice. By increasing the number of Ø 5 mm balls, 4 selectivity can be further improved (entries 5, 6). Although 40 pcs afforded close to exclusive formation of 4, 35 pcs were used in further measurements to make the effect of the other reaction parameters visible. Thus, when the reaction mixture was milled for half of the previously used time, both the conversion and S4 decreased (entry 7).

Our results obtained in batch reactions showed that a small amount of MeOH may improve the selectivity of 4 in this cascade reaction. Moreover, many of the mechanochemical reactions that have been reported up to now are not completely neat; a small amount of additional liquid with an energy mediating role is often used, which also ensures the proper mixing of the system [79,80]. By decreasing the excess of 2 and replacing the missing volume with MeOH, conversion and S4 of the mechanochemical reaction were improved (Figure 1). With as little as 1.1 eq 2 and 0.057 mL MeOH, the reaction solely afforded product 4 in the mixer mill following 180 min of grinding.

![Figure 1](image-url)

**Figure 1.** Effect of MeOH amount (▲: Conv, conversion; •: S4, selectivity of 4—both determined by GC-FID). Reaction condition: 100 mg Amberlyst® 15, 1 mmol 1, 1.5–1.1 mmol 2, total liquid volume of 0.213 mL, 35 pcs Ø 5 mm ZrO2 balls, 30 Hz, 180 min.

Decreasing either the milling time or frequency had an unfavourable effect in reactions using 100 mg Amberlyst® 15, 0.057 mL MeOH and 35 pcs of Ø 5 mm grinding balls. Thus, at least 180 min of milling at 30 Hz was necessary to achieve high conversion and up to 99% S4 (Table 4). Importantly, the reaction time can be decreased significantly compared to the magnetically stirred system (3 vs. 24 h). Although the reaction is shorter, more catalyst is demanded to achieve a good result; 50 mg Amberlyst® 15 was not enough to promote the second ring-closing step properly (Table 4, entry 7). The use of pre-milled Amberlyst® 15P (entry 3, 5) gave similar results to the commercial form in mechanochemical reactions, probably due to grinding of the bead-like Amberlyst® 15 during the initial stages of the milling process, with pre-milling thus losing its importance.
Table 4. Effect of milling time and agitation frequency in the reaction of 1 and 2.a.

| Entry | Reaction Time (min) | Agitation Frequency (Hz) | Conv (%) b | S3 (%) c | S4 (%) c |
|-------|---------------------|--------------------------|------------|----------|----------|
| 1     | 60                  | 30                       | 90         | 58       | 40       |
| 2     | 120                 | 30                       | 93         | 28       | 70       |
| 3 e   | 120                 | 30                       | 97         | 25       | 73       |
| 4     | 180                 | 30                       | 98         | -        | 99 (88) d |
| 5 e   | 180                 | 30                       | >99        | -        | 99 (92) d |
| 6     | 180                 | 20                       | 99         | 80       | 18       |
| 7 f   | 180                 | 30                       | 99         | 38       | 60       |

a Reactions were carried out using 100 mg Amberlyst® 15, 1 mmol 1, 1.1 mmol 2 and 57 µL MeOH with 35 pcs of Ø 5 mm ZrO2 grinding balls. b Conversion by GC-FID. c Selectivities of 3 and 4 by GC-FID. d In parentheses, the yield of the crystallized 4. e Reaction using 100 mg pre-milled Amberlyst® 15P. f Using 50 mg Amberlyst® 15.

Finally, a few other acidic Brønsted catalysts used in the batch system were also re-examined under mechanochemical conditions (Table 5). The reaction carried out without a catalyst gave low conversion and S4 (entry 1). Although the system warms up during the milling process, i.e., the mixture is heated up to cca 55 °C after 3 h of milling (based on our previous studies) [100], the temperature in the jar is not high enough to promote either step. The best results so far were provided by the Amberlyst® 15 used in this study (entry 2). In the magnetically stirred system, Amberlyst® XN-1010 also gave similar results; however, the mechanochemical reaction was less efficient than with the former, probably due to its lower ion-exchange capacity (Amberlyst® 15: 4.7 meq/g, Amberlyst® XN-1010: 3.3 meq/g [101,102]; entry 3). Thus, a higher amount of this material should be used. Although Nafion™ NR50 gave a similar result to the Amberlyst® resins in batch reactions at 90 °C, in the ball-milled reaction the former was much less efficient. Additionally, with the lower temperature reached in the mechanochemical system, the non-porous (and having low surface area) Nafion™ NR50 polymer was not brittle and consequently was not ground into powder. Instead, this material formed a thick, sticky paste which was not mixed properly with the reactants. The acid-treated montmorillonite (Mont K-10) mostly catalyzed the first ring-closing step in the mixer mill, which may also be attributed to the low temperature of the mixture in the milling jars.

Table 5. Influence of the catalyst in the mechanochemical reaction of 1 and 2.a.

| Entry | Catalyst | Catalyst Amount | Conv (%) b | S3 (%) c | S4 (%) c |
|-------|----------|-----------------|------------|----------|----------|
| 1     | -        | -               | 5          | 80       | 18       |
| 2     | Amberlyst® 15 | 100 mg         | 98         | -        | 99       |
| 3     | Amberlyst® XN-1010 | 100 mg       | 99         | 14       | 85       |
| 4     | Nafion™ NR50 | 85 mg (2 pcs)  | 48         | 63       | 35       |
| 5     | Mont K10  | 125 mg          | 52         | 82       | 16       |

a Reactions carried out using 1 mmol 1, 1.1 mmol 2 and 57 µL MeOH with 35 pcs Ø 3 mm ZrO2 grinding balls at 30 Hz for 180 min. b Conversion by GC-FID. c Selectivities of 3 and 4 by GC-FID.

3. Materials and Methods

The anthranilamide (1), ethyl levulinate (2), p-toluenesulfonic acid monohydrate (p-TsOH) and the applied methanol were obtained from commercial sources (Sigma-Aldrich, St. Louis, MO, USA) and used as received. The heterogeneous acid catalysts were commercial materials: Amberlyst® 15 (Sigma-Aldrich, St. Louis, MO, USA; brown-grey beads, ion-exchange capacity: 4.7 meq/g, average pore diameters 265 Å, surface area: 45–55 m²/g, [101–103]); Amberlyst® XN-1010 (Sigma-Aldrich Chem, Steighem, Germany, presently not available; dark grey beads, ion-exchange capacity: 3.3 meq/g, average pore diameters 51 Å, surface area: 540 m²/g [101,102]); Nafion™ NR50 (Sigma-Aldrich, St. Louis, MO, USA, has been discontinued; opaque white pellet, ion-exchange capacity:...
Molecules 2022, 27, 5671

≥0.8 meq/g, non-porous, surface area: <0.02 m²/g [101]); Deloxan® ASP (Degussa AG, Hanau, Germany; white powder, 0.80 mmol S/g [104]); montmorilonite K10 (Mont K10, Sigma-Aldrich, St. Louis, MO, USA) (light beige powder, surface area: 220–270 m²/g, total concentration of the acid centers 0.45 mmol/g [105]); montmorilonite KSF (Mont KSF, Sigma-Aldrich, St. Louis, MO, USA, currently is not available; off-white powder, surface area: 20–40 m²/g [106]); and Silica gel 60 (Merck Millipore, Darmstadt, Germany, white powder, particle size: 250–500 µm, pore size: 150 Å, pore volume: 1.15 mL/g). In some reactions, Amberlyst® 15 was used after pre-milling for 10 min with 30 Hz agitation frequency in a 10-mL ZrO₂ grinding jar applying 35 pcs of Ø 5 mm ZrO₂ grinding balls (Retsch GmbH, Haan, Germany).

¹H and ¹³C NMR spectra of the purified products were recorded on a Bruker Ascend 500 instrument using CDCl₃ solvent. Products were isolated by crystallization in ethyl acetate (4) or purified by flash chromatography (3). Gas-chromatographic analysis of the reaction products was carried out using an Agilent Techn. 6890 N GC-5973 MSD (GC-MSD, Agilent Co., Santa Clara, CA, US) equipped with a 30 m long HP-1MS capillary column for mass spectrometric identification of the products. For quantitative analysis, an Agilent 7890A GC-FID (GC-FID, Agilent Co., Santa Clara, CA, US) chromatograph equipped with a capillary column (HP-5 30 m, J & W from Agilent Co., Santa Clara, CA, US) was used.

3.1. Reaction of Anthranilamide and Ethyl Levulinate in the Batch System: General Procedure

The reactions were carried out in 4-mL closed glass vials immersed in a heated oil bath and the slurries were stirred magnetically (600 rpm). In a typical reaction, 1 mmol 1, 1.1–1.5 mmol 2 (0.022–0.057 mL MeOH) and the chosen catalyst were introduced into the vial and stirred at 60 or 90 °C for 24 or 48 h. Following the reactions, the products were dissolved in 3 mL MeOH, and the catalysts were separated by filtration or centrifugation. The liquid phases were analyzed by gas-chromatography using n-decane as the internal standard (GC-MSD and GC-FID). Conversions (Conv) and selectivities (S₃ and S₄) were calculated based on the relative concentrations determined from chromatograms using the formulae given in the Supplementary Materials. The products that resulted in a few reactions were purified either by crystallization in ethyl acetate (4) or by flash chromatography using hexane/ethyl acetate 1/1 as eluent (3) for the determination of the yields. The identity of the isolated products was confirmed by ¹H and ¹³C NMR spectroscopic measurements using CDCl₃ as a solvent. The experiments were repeated at least 3 times and the reproducibility of product composition was found to be within ±1%.

3.2. Reaction of Anthranilamide and Ethyl Levulinate by Ball Milling: General Procedure

The reactions were carried out in 10-mL closed grinding jars with a ZrO₂ inner coat and ZrO₂ grinding balls (Ø 3, 5, 12, 15 mm). In a typical reaction, 1 mmol 1, 1.1–1.5 mmol 2 (0.022–0.057 mL MeOH) and the chosen catalyst were introduced into the jars, and the chosen number of balls was then added to the system. The closed jars were placed into a Retsch MM400 mixer mill (Retsch GmbH, Haan, Germany) and agitated at a 30 Hz frequency for a maximum of 180 min. Following reactions, the products were dissolved in 1 mL MeOH, the jars and balls were washed twice with 1 mL MeOH and the unified liquid phase was filtrated and analyzed in the same manner as the products of the magnetically stirred reactions. The experiments were repeated at least 3 times and the reproducibility of product composition was found to be within ±1%.

Analytical data of the products:
Ethyl 3-(2-methyl-4-oxo-1,2,3,4-tetrahydroquinazolin-2-yl)propanoate (3)
Flash chromatographic separation, eluent: hexane/ethyl acetate 1/1, off-white crystals, mp 88–91 °C.
GC-FID analysis (HP-5 column): Rₚ = 47.6 min.
Flash chromatographic separation, eluent: hexane/ethyl acetate 1/1, off-white crystals, mp 88–91 °C.

3a-Methyl-2,3,3a,4-tetrahydropyrrolo[1,2-c]quinazoline-1,5-dione (4)

Separation by crystallization in ethyl acetate, white crystals, mp 162–165 °C. GC-FID analysis (HP-5 column): R_t = 52.4 min.

Ethyl 3-(2-methyl-4-oxo-1,2,3,4-tetrahydroquinazolin-2-yl)propanoate (3)

GC-FID analysis (HP-5 column): Rt= 47.6 min.

1H NMR (500 MHz, CDCl3) δ (ppm): 7.85 (d, 1H, J 7.7 Hz, Ar-H), 7.27 (m, 1H, Ar-H), 6.90 (s, 1H, N-H), 6.78 (t, 1H, J 7.7 Hz, Ar-H), 6.58 (d, 1H, J 8.0 Hz, Ar-H), 4.34 (s, 1H, N-H), 4.10 (q, 2H, J 7.1 Hz, CH2), 2.65 (m, 2H, CH2), 2.10 (m, 2H, CH2), 1.54 (s, 3H, CH3), 1.20 (t, 3H, J 7.1, CH3).

13C NMR (125 MHz, CDCl3) δ (ppm): 173.7, 164.4, 145.9, 134.0, 128.3, 118.6, 114.5, 114.1, 69.9, 60.8, 36.6, 29.1, 29.0, 14.1.

3a-Methyl-2,3,3a,4-tetrahydropyrrolo[1,2-c]quinazoline-1,5-dione (4)

Separation by crystallization in ethyl acetate, white crystals, mp 162–165 °C.

GC-FID analysis (HP-5 column): R_t = 52.4 min.

GC-MSD m/z (rel. int.): 216(M+, 6), 201(24), 1173(35), 161(6), 132(6), 90(6), 42(2).

1H NMR (500 MHz, CDCl3) δ (ppm): 8.16 (d, 1H, J 8.1 Hz, Ar-H), 8.07 (d, 1H, J 7.8 Hz, Ar-H), 7.89 (s, 1H, N-H), 7.59 (m, 1H, Ar-H), 7.29 (m, 1H, Ar-H), 2.70 (m, 2H, CH2), 2.39 (m, 2H, CH3), 1.57 (s, 3H, CH3).

13C NMR (125 MHz, CDCl3) δ (ppm): 171.6, 163.3, 135.8, 133.8, 128.3, 125.0, 120.7, 119.5, 76.7, 74.5, 32.9, 30.0, 26.9.

4. Conclusions

In the present study, we have developed a method to increase the sustainability of the preparation of a pyrrolo[1,2-a]quinazoline-1,5-dione derivative through a one-pot cascade reaction occurring by reacting anthranilamide and ethyl levulinate. The application of a heterogeneous acid catalyst and mechanochemical activation in the two-step reaction was successful, resulting in a decrease in the necessary reaction time from 24 h in a magnetically stirred batch system to as little as three hours. The reaction was carried out in a ball mill via liquid-assisted grinding with only a minor excess of ethyl levulinate and using a slight amount of methanol. A polystyrene-based sulfonic acid-functionalized catalyst, i.e., Amberlyst® 15, provided the best results both in the batch and in the mechanochemical reactions. In the latter system, the use of an acid catalyst with appropriate properties was essential, as the heat generated by the collision and friction of the grinding media was not sufficient to promote the second ring-closing step thermally.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/molecules27175671/s1, General formulae; Figure S1: Effect of temperature on the reaction of anthranilamide (1) with ethyl levulinate (2) in the batch system; Figure S2: Effect of the catalyst amount on the reaction of anthranilamide (1) with ethyl levulinate (2) in the batch system; 1H and 13C NMR spectra of the isolated products; Chromatograms and mass spectra of the products.

Author Contributions: V.J.K. and G.S. contributed equally to the presented research. All authors have read and agreed to the published version of the manuscript.

Funding: The Hungarian Science Foundation funded this research, grant number K138871.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.
Data Availability Statement: The data presented in this study are available on request from the corresponding author.

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

Sample Availability: Not available.

References

1. Frank, É.; Szőllősi, G. Nitrogen-Containing Heterocycles as Significant Molecular Scaffolds for Medicinal and Other Applications. Molecules 2021, 26, 4617. [CrossRef]

2. Alaimo, R.J. Antibacterial 2,3-Dihydro-2-(5-nitro-2-thienyl)quinazolin-4(1H)-ones. J. Med. Chem. 1972, 15, 335–336. [CrossRef]

3. Parish, H.A., Jr.; Gilliom, R.D. Syntheses and Diuretic Activity of 1,2-Dihydro-2-(3-pyridyl)-3H-pyrido[2,3-d]pyrimidin-4-one and Related Compounds. J. Med. Chem. 1982, 25, 98–102. [CrossRef] [PubMed]

4. Hour, M.-J.; Huang, L.-J.; Kuo, S.-C.; Xia, Y.; Bastow, K.; Nakashashi, Y.; Hamel, E.; Lee, K.-H. 6-Alkylamino- and 2,3-Dihydro-3′-methoxy-2-phenyl-4-quinazolines and Related Compounds: Their Synthesis, Cytotoxicity, and Inhibition of Tubulin Polymerization. J. Med. Chem. 2000, 43, 4479–4487. [CrossRef] [PubMed]

5. Sharma, P.C.; Kaur, G.; Pahwa, R.; Sharma, A.; Rajak, H. Quinazolone Analogs as Potential Therapeutic Agents. Curr. Med. Chem. 2011, 18, 4786–4812. [CrossRef]

6. He, D.; Wang, M.; Zhao, S.; Shu, Y.; Zeng, H.; Xiao, C.; Lu, C.; Liu, Y. Pharmaceutical prospects of naturally occurring quinazolone and its derivatives. Fitoterapia 2017, 119, 136–149. [CrossRef] [PubMed]

7. Hameed, A.; Al-Rashida, M.; Uroos, M.; Ali, S.A.; Arshia; Ishitaq, M.; Khan, K.M. Quinazoline and quinazolone as important medicinal scaffolds: A comparative patent review (2011–2016). Expert Opin. Ther. Patents 2018, 28, 281–297. [CrossRef]

8. Wahan, S.K.; Sharma, B.; Chawla, P.A. Medicinal perspective of quinazolone derivatives: Recent developments and structure-activity relationship studies. J. Heterocycl. Chem. 2022, 59, 239–257. [CrossRef]

9. Badolato, M.; Aiello, F.; Neamti, N. 2,3-Dihydroquinazolin-4(1H)-one as a privileged scaffold in drug design. RSC Adv. 2018, 8, 20894–20921. [CrossRef] [PubMed]

10. Yale, H.L.; Kalkstein, M. Substituted 2,3-Dihydro-4(1H)-quinazolines. A New Class of Inhibitors of Cell Multiplication. J. Med. Chem. 1967, 10, 334–336. [CrossRef] [PubMed]

11. Chavan, S.P.; Sivappa, R. A short and efficient general synthesis of luotonin A, B and E. J. Comb. Chem. 2012, 14, 1269–1273. [CrossRef] [PubMed]

12. Esfandiari, S.; Maghsoudlou, M.T.; Habibi-Khorassani, S.M.; Kiae, S.; Aboonajmi, J. Malonic acid as a catalyst for efficient and simple synthesis of 2,3-dihydroquinazolin-4(1H)-one in green solvent. Iranian J. Org. Chem. 2012, 4, 827–830.

13. Khadem, S.; Hazeri, N.; Maghsoudlou, M.T. Green protocol for synthesis of 2,3-dihydroquinazolin-4(1H)-ones: Lactic acid as catalyst under solvent-free condition. Res. Chem. Intermed. 2016, 42, 6381–6390. [CrossRef]

14. Sarfraz, M.; Sultana, N.; Rashid, U.; Akram, M.S.; Sadiq, A.; Tariq, M.I. Synthesis, biological evaluation and docking studies of 2,3-dihydroquinazolin-4(1H)-ones derivatives as inhibitors of cholinesterases. Bioorg. Chem. 2017, 70, 237–244. [CrossRef]

15. Sharma, S.D.; Kaur, V. Synthesis of 3-Oxa- and 3-Aza-1-dethiacepham Analogs. Synthesis 1989, 677–680. [CrossRef]

16. Bhavani, A.K.D.; Reddy, P.S.N. Synthesis of Some Tetrahydro-3′,3′-bisquinazolin-4,4′-diones. Org. Prep. Proc. Int. 1992, 24, 1–5. [CrossRef]

17. Naleway, J.J.; Fox, C.M.J.; Robinhold, D.; Terpentschnig, E.; Olson, N.A.; Haugland, R.P. Synthesis and Use of New Fluorogenic Anthranilamide and 3-Amino-2-carbamoylthiophene with Ketones. Formation of Tetrahydroquinazolines and Their Thiophene Isosteres. J. Heterocycl. Chem. 1998, 35, 1269–1273. [CrossRef]

18. Bunce, R.A.; Nammlawar, B. New Conditions for Synthesis of (±)-2-Monosubstituted and (±)-2,2-Disubstituted 2,3-Dihydro-4(1H)-quinazolines from 2-Nitro and 2-Aminobenzamide. J. Heterocycl. Chem. 2011, 48, 991–997. [CrossRef]

19. Zoubal, V.; Grasso, S.; Micale, N.; Zuccalà, G.; Menitt, F.S.; Ferreri, G.; Di Sarro, G.; De Micheli, C. 1-Aryl-6,7-methylenedioxy-3H-quinazolin-4(1H)-ones as Anticonvulsant Agents. Bioorg. Med. Chem. Lett. 2003, 13, 4427–4430. [CrossRef]

20. Labade, V.B.; Shirade, P.V.; Shingare, M.S. A facile and rapid access towards the synthesis of 2,3-dihydroquinazolin-4(1H)-ones. Tetrahedron Lett. 2013, 54, 5778–5780. [CrossRef]

21. Chen, J.X.; Wu, H.Y.; Su, W.K. A facile synthesis of 2,3-dihydro-2-aryl-4(1H)-quinazolines catalyzed by scandium(III) triflate. Chin. Chem. Lett. 2007, 18, 536–538. [CrossRef]

22. Wang, X.-S.; Yang, K.; Zhou, J.; Tu, S.-J. Facile Method for the Combinatorial Synthesis of 2,2-Disubstituted Quinazolin-4(1H)-one Derivatives Catalyzed By Iodine in Ionic Liquids. J. Comb. Chem. 2010, 12, 417–421. [CrossRef] [PubMed]

23. Abdollahi-Alibeik, M.; Shabani, E. Synthesis of 2,3-dihydroquinazolin-4(1H)-ones catalyzed by zirconium (IV) chloride as a mild and efficient catalyst. Chin. Chem. Lett. 2011, 22, 1163–1166. [CrossRef]

24. Englund, E.E.; Neumann, S.; Eiseveld, E.; McCoy, J.G.; Titus, S.; Zheng, W.; Southall, N.; Shinn, P.; Leister, W.; Thomas, C.J.; et al. The synthesis and evaluation of dihydroquinazolin-4-ones and quinazolin-4-ones as thyroid stimulating hormone receptor agonists. Med. Chem. Commun. 2011, 2, 1016–1020. [CrossRef] [PubMed]

25. Shang, Y.-H.; Fan, L.-Y.; Li, X.-X.; Liu, M.-X. Y(OTf)3-catalyzed heterocyclic formation via aerobic oxygenation: An approach to dihydro quinazolines and quinazolines. Chin. Chem. Lett. 2015, 26, 1355–1358. [CrossRef]
27. Rajaka, L.; Penumati, N.R.; Nagaiah, K.; Poornachandra, Y.; Kumar, C.G. Convenient and Scalable Synthesis of 2,3-Dihydroquinazolin-4(1H)-one Derivatives and Their Anticancer Activities. *Synth. Commun.* 2015, 45, 1893–1901. [CrossRef]

28. Ramesh, N.; Rao, M.G.; Varala, R.; Rao, V.U.; Babu, B.H. Mercuric chloride catalyzed synthesis of some anticancer 2-aryl-2,3-dihydroquinazolin-4(1H)-ones. *Med. Chem. Res.* 2016, 25, 1945–1951. [CrossRef]

29. Sivaguru, P.; Parameswaran, K.; Lalitha. A Synthesis of novel eight-membered dibenzo[b,f][1,5]oxazocin-6-ones. *Tetrahedron Lett.* 2016, 57, 2549–2553. [CrossRef]

30. Luo, Y.; Wu, Y.; Wang, Y.; Sun, H.; Xie, Z.; Zhang, W.; Gao, Z. Ethanol promoted titanocene Lewis acid catalyzed synthesis of quinazoline derivatives. *RSC Adv.* 2016, 6, 66074–66077. [CrossRef]

31. Shaabani, A.; Maleki, A.; Mofakham, H. Click Reaction: Highly Efficient Synthesis of 2,3-Dihydroquinazolin-4(1H)-ones. *Synth. Commun.* 2008, 38, 3751–3759. [CrossRef]

32. Li, S.-C.; Jhang, W.-F.; Liou, T.-J.; Yang, D.-Y. Photochemical synthesis of indazolo[3,2-b]quinazolines and their redox-switching properties. *Dyes Pigment.* 2015, 114, 259–266. [CrossRef]

33. Qiao, R.Z.; Xu, B.L.; Wang, Y.H. A facile synthesis of 2-substituted-2,3-dihydro-4(1H)-quinazolinones under Solvent-free Conditions. *Chin. Chem. Lett.* 2009, 20, 3447–3450. [CrossRef]

34. Rostamizadeh, S.; Amani, A.M.; Aryan, R.; Ghaieni, H.R.; Shadjou, N. Synthesis of New 2-Aryl Substituted 2,3-Dihydroquinazolinones (DHQZs) and Bis 3-Indolyl Methanes (BIMs). *Appl. Organometal. Chem.* 2020, 34, e4431. [CrossRef]

35. Xie, Z.-B.; Zhang, S.-G.; Jiang, G.-F.; Sun, D.-Z.; Le, Z.-G. The green synthesis of 2,3-dihydroquinazolin-4(1H)-ones. *RSC Adv.* 2013, 3, 407–412. [CrossRef]

36. Dindulkar, S.D.; Oh, J.; Arole, V.M.; Jeong, Y.T. Supported ceric ammonium nitrate: A highly efficient catalytic system for the synthesis of quinazolin-4(3H)-ones. *Magn. Reson. Chin.* 2008, 46, 1119–1126. [CrossRef]

37. Roy, A.D.; Jayalakshmi, K.; Dasgupta, S.; Roy, R.; Mukhopadhyay, B. Real time HR-MAS NMR: Application in reaction optimization, mechanism elucidation and kinetic analysis for heterogeneous reagent catalyzed small molecule chemistry. *Green Chem. Lett. Rev.* 2014, 656–658. [CrossRef]

38. Shaterian, H.R.; Oveisi, A.R. PPA-SiO$_2$ as a Heterogeneous Catalyst for Efficient Synthesis of 2-Substituted-1,2,3,4-tetrahydro-4(1H)quinazolinones under Solvent-Free Conditions. *Chin. J. Chem.* 2014, 32, 656–658. [CrossRef]

39. Dar, B.A.; Sahu, A.K.; Patidar, P.; Sharma, P.R.; Mupparapu, N.; Vyas, D.; Maity, S.; Sharma, M.; Singh, B. Heteropolyacid-clay nano-composite as a novel heterogeneous catalyst for the synthesis of 2,3-dihydroquinazolinones. *J. Mol. Catal. A: Chem.* 2015, 419, 407–412. [CrossRef]

40. Dindulkar, S.D.; Oh, J.; Arole, V.M.; Jeong, Y.T. Supported ceric ammonium nitrate: A highly efficient catalytic system for the synthesis of diversified 2,3-substituted-2,3-dihydroquinazolin-4(1H)-ones. *Comptes Rendus Chim.* 2014, 17, 971–979. [CrossRef]

41. Safari, J.; Gandomi-Ravandi, S. Efficient synthesis of 2-aryl-2,3-dihydroquinazolin-4(1H)-ones in the presence of nanocomposites under microwave irradiation. *J. Mol. Catal. A: Chem.* 2014, 390, 1–6. [CrossRef]

42. Haravi, F.; Ghorbani-Choghamarani, A.; Nikpour, F. Synthesis and characterization of nickel complex anchored onto MCM-41 as a novel and reusable nanocatalyst for the efficient synthesis of 2,3-dihydroquinazolin-4(1H)-ones. *Microporous Mesoporous Mat.* 2016, 24, 26–35. [CrossRef]

43. Kausar, N.; Roy, I.; Chattopadhyay, D.; Das, A.R. Synthesis of 2,3-dihydroquinazolinones and quinazolin-4(3H)-ones catalyzed by graphene oxide nanosheets in an aqueous medium: “on-water” synthesis accompanied by carbocatalysis and selective C-C bond cleavage. *RSC Adv.* 2016, 6, 22320–22330. [CrossRef]

44. Shiri, L.; Ghorbani-Choghamarani, A.; Kazemi, M. Cu(II) immobilized on Fe$_3$O$_4$-diethylenetriamine: A new magnetically recoverable catalyst for the synthesis of 2,3-dihydroquinazolin-4(1H)-ones and oxidative coupling of thiols. *Appl. Organometal. Chem.* 2017, 31, e3956. [CrossRef]

45. Mirjalili, B.B.F.; Bamoniri, A.; Azad, S. Synthesis of 2,3-dihydroquinazolin-4(1H)-ones catalyzed by nano-Fe$_3$O$_4$/TiCl$_4$/cellulose as a bio-based magnetic catalyst. *J. Iran. Chem. Soc.* 2017, 14, 47–55. [CrossRef]

46. Radfar, I.; Miraki, M.K.; Ghandi, L.; Esfandiary, N.; Abbasi, A.; Karimi, M.; Heydar, A. BF$_3$-grafted Fe$_3$O$_4$@Sucrose nanoparticles as a highly-efficient acidic catalyst for syntheses of Dihydroquinazolines (DHQZs) and Bis 3-Indolyl Methanes (BIMs). *Appl. Organometal. Chem.* 2018, 32, e4431. [CrossRef]

47. Efraf, M.A.; Akhlaghinia, B.; Ghodsinia, S.S.E. An Efficient Green Protocol for Synthesis of 2,3-Dihydroquinazolin-4(1H)-ones Using SBA-16/GPTMS-TSC-Cu under Solvent-Free Conditions. *ChemistrySelect* 2020, 5, 2306–2316. [CrossRef]

48. Subba Reddy, B.V.; Venkateswarlu, A.; Madan, C.; Vinu, A. Cellulose-SO$_2$H: An efficient and biodegradable solid acid for the synthesis of quinazolin-4(3H)-ones. *Tetrahedron Lett.* 2011, 52, 1891–1894. [CrossRef]

49. Ghashang, M.; Mansoor, S.S.; Aswin, K. Synthesis of 2,3-dihydroquinazolin-4(1H)-ones catalyzed by succinimide-N-sulfonic acid as a mild and efficient catalyst. *Res. Chem. Intermed.* 2015, 41, 3447–3460. [CrossRef]

50. Ghorbani-Choghamarani, A.; Azadi, G. Synthesis, characterization, and application of Fe$_3$O$_4$-SA-PPCA as a novel nanomagnetic reusable catalyst for the efficient synthesis of 2,3-dihydroquinazolin-4(1H)-ones and polyhydroquinolines. *RSC Adv.* 2015, 5, 9752–9758. [CrossRef]

51. Rao, A.V.D.; Vy.kuntoswara Rao, B.P.; Bhaskarkumar, T.; Jogdand, N.R.; Kalita, D.; Lilakar, J.K.D.; Siddaiha, V.; Sanasi, P.D.; Raghunadh, A. Sulfonic acid functionalized Wang resin (Wang-OSO$_3$H) as polymeric acidic catalyst for the eco-friendly synthesis of 2,3-dihydroquinazolin-4(1H)-ones. *Tetrahedron Lett.* 2015, 56, 4714–4717. [CrossRef]
52. Ghorbani-Choghamarani, A.; Tahmasbi, B. The first report on the preparation of boehmite silica sulfuric acid and its application in some multicomponent organic reactions. New J. Chem. 2016, 40, 1205-1212. [CrossRef]

53. Hajami, M.; Ghorbani-Choghamarani, A.; Ghafouri-Nejad, R.; Tahmasbi, B. Efficient preparation of boehmite silica dopamine sulfamic acid as a novel nanostructured compound and its application as a catalyst in some organic reactions. New J. Chem. 2016, 40, 3066-3074. [CrossRef]

54. Bharate, S.B.; Mpparapu, N.; Manda, S.; Bharate, J.B.; Mudududdla, R.; Yadav, R.R.; Vishwakarma, R.A. Efficient synthesis of 2,3-dihydroquinazolin-4(1H)-ones using heterogeneous solid acid catalysts: Unexpected formation of 2,3-dihydro-2-(4-(tetrahydro-2H-pyran-2-yl)oxy)butyl)quinazolin-4(1H)-one. Arkivoc 2012, viii, 308-318. [CrossRef]

55. Murthy, P.V.N.S.; Ramabu, D.; Krishna, G.R.; Reddy, C.M.; Prasad, K.R.S.; Rao, M.V.B.; Pal, M. Amberlyst-15 mediated synthesis of 2-substituted 2,3-dihydroquinazolin-4(1H)-ones and their crystal structure analysis. Tetrahedron Lett. 2012, 53, 863-867. [CrossRef]

56. Rambabu, D.; Kumar, S.K.; Sreenivas, B.Y.; Sandara, S.; Kandaale, A.; Misra, P.; Rao, M.V.B.; Pal, M. Ultrasound-based approach to spiro-2,3-dihydroquinazolin-4(1H)-ones: Their in vitro evaluation against chorismate mutase. Tetrahedron Lett. 2013, 54, 495-501. [CrossRef]

57. Cai, G.; Xu, X.; Li, Z.; Weber, W.P.; Lu, P. A One-Pot Synthesis of 2-Aryl-2,3-dihydro-4(1H)-quinazolinones by use of Samarium Iodide. J. Heterocycl. Chem. 2002, 39, 1271-1272. [CrossRef]

58. Su, W.; Yang, B. Reductive Cyclization of Nitro and Azide Compounds with Aldehydes and Ketones Promoted by Metallic Samarium and Catalytic Amount of Iodide. Aust. J. Chem. 2002, 55, 695-697. [CrossRef]

59. Shi, D.; Rong, L.; Wang, J.; Zhuang, Q.; Wang, X.; Hu, H. Synthesis of quinazolin-4(3H)-ones and 1,2-dihydroquinazolin-4(3H)-ones with the aid of a low-valent titanium reagent. Tetrahedron Lett. 2003, 44, 3199-3201. [CrossRef]

60. Surpur, M.P.; Singh, P.R.; Patil, S.B.; Samant, S.D. Expeditious One-Pot and Solvent-Free Synthesis of Dihydroquinazolin-4(1H)-ones in the Presence of Microwaves. Synth. Commun. 2007, 37, 1965-1970. [CrossRef]

61. Rostamizadeh, S.; Amani, A.M.; Mahdaviania, G.H.; Sephehrani, H.; Ebrahim, S. Synthesis of Some Novel 2-Aryl-Substituted 2,3-Dihydroquinazolin-4(1H)-ones under Solvent-Free Conditions Using MCM-41-SO3H as a Highly Efficient Sulfonic Acid. Synthesis 2010, 1356-1360. [CrossRef]

62. Tamaddon, F.; Pouramini, F. Amberlyst A26 OH as a Recyclable Catalyst for Hydration of Nitriles and Water-Based Synthesis of 4(1H)-Quinazolinones from 2-Aminobenzonitrile and Carbonyl Compounds. Synlett 2014, 25, 1127-1131. [CrossRef]

63. Shaterian, H.R.; Rigi, F. An efficient synthesis of quinazoline and xanthene derivatives using starch sulfate as a biodegradable solid acid catalyst. Res. Chem. Intermed. 2015, 41, 721-738. [CrossRef]

64. Wang, X.-S.; Yang, K.; Zhang, M.-M.; Yao, C.-S. Synthesis of 2-Arylquinazolin-4(3H)-one Derivatives Catalyzed by Iodine in [bmim][BF4]. Synth. Commun. 2010, 40, 2633-2646. [CrossRef]

65. Nagasawa, Y.; Matsusaki, Y.; Nobuta, T.; Tada, N.; Miura, T.; Itoh, A. Aerobic photooxidative synthesis of 2-aryl-4-quinazolinones from aromatic aldehydes and aminobenzamide using catalytic amounts of molecular iodine. RSC Adv. 2015, 5, 63952–63954. [CrossRef]

66. Feng, E.; Zhou, Y.; Zhang, D.; Zhang, L.; Sun, H.; Jiang, H.; Liu, H. Gold(I)-Catalyzed Tandem Transformation: A Simple Approach for the Synthesis of Pyrrolo[2,1-a][1,3]benzoxazines and Pyrrolo[2,1-a]quinazolinones. J. Org. Chem. 2010, 75, 3274–3282. [CrossRef]

67. Wang, M.; Dou, G.; Shi, D. Efficient and Convenient Synthesis of Pyrrolo[1,2-a]quinazoline Derivatives with the Aid of Tin(II) Chloride. J. Comb. Chem. 2010, 12, 582–586. [CrossRef]

68. Zhao, X.; Shi, D.-Q. An Efficient Synthesis of Pyrrolo[1,2-a]quinazolin-5(1H)-one Derivatives with the Aid of Low-Valent Titanium Reagent. J. Heterocycl. Chem. 2011, 48, 634–638. [CrossRef]

69. Safai, H.R.; Shekouhy, M.; Khademi, S.; Rahamanian, V.; Safaei, M. Diversity-oriented synthesis of quinazoline derivatives using zirconium tetraisodododecylsulfinate ([Zr(DS)4]) as a reusable Lewis acid-surfactant-combined catalyst in tap water. J. Ind. Eng. Chem. 2014, 20, 3019–3024. [CrossRef]

70. Lu, L.; Yang, K.; Zhang, M.-M.; Wang, X.-S. An Efficient Synthesis of Pyrrolo[1,2-a]quinazoline Derivatives in Ionic Liquid Catalyzed by Iodine. J. Heterocycl. Chem. 2014, 51, 841–845. [CrossRef]

71. Zou, X.; Zhu, C.; Wang, Q.; Yang, G. Catalytic dehydration of hexose sugars to 5-hydroxymethylfurfural. Biofuels Bioprod. Biorefining 2019, 13, 153–173. [CrossRef]

72. Nzediegwu, E.; Dumont, M.-J. Chemo-Catalytic Transformation of Cellulose and Celluliosic-Derived Waste Materials into Platform Chemicals. Waste Biomass Valorization 2021, 12, 2825–2851. [CrossRef]

73. Castro, G.A.D.; Fernandes, S.A. Microwave-assisted synthesis of levulinic esters as biofuel precursors using calix[4]aren as an organocatalyst under solvent-free conditions. Sustain. Energ. Fuels 2021, 5, 108–111. [CrossRef]

74. Zhang, W.; Cue, B.W. (Eds.) Green Techniques for Organic Synthesis and Medicinal Chemistry, 2nd ed.; John Wiley & Sons, Inc.: Hoboken, NJ, USA, 2018.

75. Protti, S.; Palmieri, A. (Eds.) Sustainable Organic Synthesis: Tools and Strategies; Royal Society of Chemistry: London, UK, 2022.

76. James, S.L.; Adams, C.J.; Bolm, C.; Braga, D.; Collier, P.; Fršičič, T.; Grepioni, F.; Harris, K.D.M.; Hyett, G.; Jones, W.; et al. Mecharnochemistry: Opportunities for new and cleaner synthesis. Chem. Soc. Rev. 2012, 41, 413–447. [CrossRef]

77. Wang, G.-W. Mecharnochemical organic synthesis. Chem. Soc. Rev. 2013, 42, 7668–7700. [CrossRef]
87. Dekamin, M.G.; Eslami, M. Highly efficient organocatalytic synthesis of diverse and densely functionalized 2-amino-3-cyano-4-
pyrans under mechanochemical ball milling. *Green Chem.*, 2014, 16, 4914–4921. [CrossRef]

88. Gaudino, E.C.; Tagliapietra, S.; Mantegna, S.; Cravotto, G. Mechanochemical and sonochemical heterocyclizations. *Chem. Heterocycl. Compds.* 2016, 52, 856–865. [CrossRef]

89. El-Sayed, T.H.; Aboelnaga, A.; El-Atawy, M.A.; Hagar, M. Ball Milling Promoted N-Heterocycles Synthesis. *Molecules* 2018, 23, 1348. [CrossRef] [PubMed]

90. Wang, M.; Gao, J.J.; Song, Z.G.; Wang, L. Cerium(IV) ammonium nitrate catalyzed green synthesis of 2,3-dihydroquinazolino-
4(1H)-ones using a grinding technique. *Chem. Heterocycl. Compds.* 2011, 47, 851–855. [CrossRef]

91. Ding, Q.-S.; Zhang, J.-L.; Chen, J.-X.; Liu, M.-C.; Ding, J.-C.; Wu, H.-Y. Tandem Synthesis of 2,3-Dihydroquinazolin-4(1H)-ones on Grind under Solvent-Free Conditions. *J. Heterocycl. Chem.* 2012, 49, 375–380. [CrossRef]

92. Wang, M.; Gao, J.; Song, Z.; Wang, L. Cerous Methanesulfonate Catalyzed Facile Synthesis of 2-Substituted-2,3-dihydro-4(1H)-quinazolinones by Grinding Technique. *J. Heterocycl. Chem.* 2012, 49, 1250–1253. [CrossRef]

93. Sharma, R.; Pandey, A.K.; Chauhan, P.M.S. A Greener Protocol for Accessing 2,3-Dihydro/spiroquinazolin-4(1H)-ones: Natural Acid-SDS Catalyzed Three-Component Reaction. *Synlett* 2012, 23, 2209–2214. [CrossRef]

94. Wang, M.; Gao, J.-J.; Song, Z.-G.; Wang, L. Synthesis of 2-Substituted-2,3-dihydro-4(1H)-quinazolinones using Sodium Bisulfate as a Catalyst by the Grinding Technique. *Org. Prep. Proceed. Int.* 2012, 44, 159–163. [CrossRef]

95. Miklós, F.; Hum, V.; Fülöp, F. Eco-friendly syntheses of 2,2-disubstituted- and 2-Spiroquinazolinones. *Arkivoc* 2014, vi, 25–37. [CrossRef]

96. Magyar, T.; Miklós, F.; Lázár, L.; Fülöp, F. Synthesis of 2-(hetero)arylquinazolinones in aqueous media. *Arkivoc* 2016, vi, 247–258. [CrossRef]

97. Szöllösi, G. Asymmetric one-pot reactions using heterogeneous chemical catalysis: Recent steps towards sustainable processes. *Catal. Sci. Technol.* 2018, 8, 389–422. [CrossRef]

98. Byrne, F.P.; Jin, S.; Paggiola, G.; Petchey, T.H.M.; Clark, J.H.; Farmer, T.J.; Hunt, A.J.; McElroy, C.R.; Sherwood, J. Tools and techniques for solvent selection: Green solvent selection guides. *Sustain. Chem. Process.* 2016, 4, 7. [CrossRef]

99. kolcsár, V.J.; szöllösi, G. mechanochemical, water-assisted asymmetric Transfer hydrogenation of Ketones using Ruthenium Catalyst. *ChemCatChem* 2012, 23, 2209–2214. [CrossRef]

100. Kolcsár, V.J.; Szöllösi, G. Ru-catalyzed mechanochemical asymmetric transfer hydrogenations in aqueous media using chitosan as chiral source. *Mol. Catal.* 2022, 520, 112162. [CrossRef]

101. Lee, S.Y.; Kim, J.C.; Lee, J.S.; Kim, Y.G. Carbonylation of Formaldehyde over Ion Exchange Resin Catalysts. 1. Batch Reactor Studies. *Ind. Eng. Chem. Res.* 1993, 32, 253–259. [CrossRef]

102. Park, H.-S.; Ihm, S.-K. Alkylation of benzene with 1-dodecene by macroreticular resin catalysts. *Korean J. Chem. Eng.* 1985, 2, 69–74. [CrossRef]

103. Pal, R.; Sarkar, T.; Khasnobis, S. Amberlyst-15 in organic synthesis. *Arkivoc* 2012, i, 570–609. [CrossRef]

104. Fraile, J.M.; Saavedra, C.J. Application of Heterogeneous Catalysts in the First Steps of the Oseltamivir Synthesis. *Catalysts* 2017, 7, 393. [CrossRef]

105. Kornas, A.; Śliwa, M.; Ruggiero-Mikołajczyk, M.; Samson, K.; Podobiński, J.; Karcz, R.; Duraczynska, D.; Rutkowska-Zbik, D.; Grabowski, R. Direct hydrogenation of CO2 to dimethyl ether (DME) over hybrid catalysts containing CuO/ZrO2 as a metallic function and polyolycyclic acids as an acidic function. *React. Kin. Mech. Catal.* 2020, 130, 179–194. [CrossRef]

106. Habibi, D.; Marvi, O. Montamorillonite KSF clay as an efficient catalyst for the synthesis of 1,4-dioxo-3,4-dihydropthalazine-2(1H)-carboxamides and -carbothioamides under solvent-free conditions using microwave irradiation. *Catal. Commun.* 2007, 8, 127–130. [CrossRef]