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Application of Bertagnini's Salts in a Mechanochemical Approach Toward Aza-Heterocycles and Reductive Aminations via Imine Formation

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Abstract: Our research has demonstrated that mechanochemical activation is more effective with solid reagents. We have showcased the practicality of Bertagnini's salts, also called aldehyde-bisulfite adducts, which are crystalline, simplifying preparation and storage. These salts are stable substitutes for liquid aldehydes and ketones that have been employed in reductive amination, synthesizing aza-heterocycles and hydrazones within mechanochemistry. The technique's effectiveness broadens the substrate scopes, simplifies purification, reduces reaction times, and yields the desired products ranging from 38–91%. Additionally, the thermal stability of the bisulfite adducts has been confirmed through TGA (Thermogravimetric analysis) analysis.

Keywords: Mechanochemistry; Aza-heterocycles; Bertagnini's salts; "aldehyde *solid surrogate*," aldehyde-bisulfite adducts; *beat-and-heat*

Introduction

Aldehydes and ketones are undeniably deemed to be two of the most harnessed chemical compounds in organic synthesis. Their versatility extends across a broad spectrum,[1] encompassing straightforward and intricate reactions, rendering them an exceptional adaptable tool for shaping molecular structures.[2] For instance, their reactivity seamlessly fits into iminium[3] and enamine[4] catalysis, leading to the stereoselective assembly of molecular frameworks that otherwise might be inaccessible. Likewise, both are pivotal in synthesizing heterocyclic compounds,[5] particularly those incorporating nitrogen.[6] This specific facet places these compounds at the core of organic and pharmaceutical synthetic routes, where their diverse reactivity facilitates the development of unique and consolidated strategies. Overall, aldehydes and ketones are the bedrock for formulating diverse reaction strategies and are essential for the ongoing progress in organic synthesis.

Even though these carbonyl compounds have exceptional chemical properties, their utilization comes with many challenges. The most significant issues are their tendency to participate in self-condensation reactions and the spontaneous aerobic oxidation of aldehydes when repeatedly exposed to air. Moreover,

low molecular weight aldehydes, being volatile, represent a substantial safety hazard for operators. As a result, addressing this issue requires taking additional measures, such as workup procedures or, in some instances, distillation, which significantly wastes time, energy, and chemicals.

Bertagnini's salts, also known as aldehyde-bisulfite adducts, can partially address the concern. These adducts were first discovered in the 1850s and were primarily used to isolate aldehydes from reaction mixtures as a purification technique.[7] Although they were eventually phased out, they have recently regained interest, particularly as a "*solid surrogate*" to aldehydes in specific organic reactions. Bertagnini's salts[8] exhibit a reactivity comparable to aldehydes yet they offer enhanced stability against moisture and air exposure, maintaining their integrity over extended periods. Furthermore, their scope has been expanded to encompass specific ketones, enabling access to bisulfite-adducts with a greater reactivity than their corresponding carbonyl counterparts. It's worth noting that Bertagnini's salts, like many chemical compounds, can be challenging to dissolve in environmentally friendly solvents commonly used in modern applications. Consequently, using bisulfite adducts may necessitate increased solvent volumes, extended reaction times, and higher temperatures to enhance the overall outcomes.[9]

In response to these challenges, mechanochemistry[10] has emerged as an efficient[11] and environmentally friendly technique[12] for synthesizing valuable compounds in the solid state,[13] entirely devoid of the need for solvents.[14] This makes it an ideal choice for both academic and industrial applications.[15]

However, in those cases where dry grinding proves ineffective, mechanochemistry provides, as an alternative method, the Liquid Assisted Grinding (LAG) conditions,[16] which entails the addition of a few microliters of an external liquid, thereby upholding environmental sustainability. It improves the system's rheological properties and promotes enhanced contact at the interfaces of the powdered reagents, resulting in high reaction efficiency with less waste production. Noticeably, mechanochemistry aligns even more closely with its fundamental principles when using solid surrogates of liquid aldehydes and ketones, ensuring that the kinetic energy delivered by the milling ball is efficiently transferred to a solid matter. Under LAG conditions, we can modify the mechanochemical reactivity of liquid aldehydes due to the solid nature of Bertagnini's salts used as aldehyde surrogates.

This research aims to comprehensively investigate the solvent-free applications of aldehyde- and ketone-based reactions, utilizing Bertagnini's salts as solid precursors for diverse products through the ball milling technology. These reactions have been carefully designed to prioritize the synthesis of aza heterocycles, such as benzimidazoles, dihydro-perimidines, and perimidines, which recall drug-like molecular structures or play a crucial role in developing optoelectronic and photochromic materials. This methodology has also proven effective for reductive aminations and hydrazone synthesis.

Results and Discussion

Initially, we examined the thermal properties of Bertagnini's salts before delving into their reactivity in mechanochemistry. Our main aim in this preliminary investigation was to determine if the milling process could cause the melting of Bertagnini's salts, creating a molten phase that might enhance the interaction between the chemical species. We performed Differential Scanning Calorimetry (DSC) analyses of selected Bertagnini's salts (see Figure 1). The findings showed that the melting points were considerably higher than the 100–120 °C range, indicating that Bertagnini's salts remain solids throughout the mechanochemical reaction (the DSC experimental plots are presented in the supplementary information). Once we had established this, we directed our attention towards synthesizing various moieties.

Benzimidazoles

The significance of benzimidazole and its analogues[17] (Figure 2) in the fields of natural products,[18] pharmaceutical,[19] and biological chemistry[20] highlights the importance of their synthesis. However, conventional methods[21] often require catalysts, oxi-

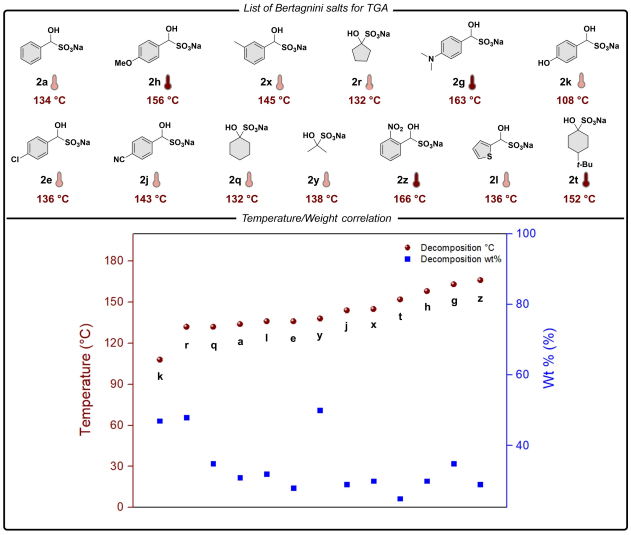


Figure 1. Bertagnini's salts and their decomposition concerning temperature.

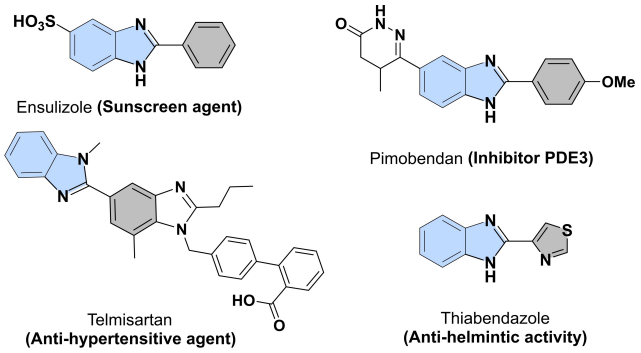


Figure 2. Benzimidazoles contain some biologically active molecules.

dants, or high reaction temperatures. We employed Bertagnini's salts to achieve rapid and efficient benzimidazole synthesis through a ball milling protocol conducted at room temperature to address these challenges.

To fine-tune the reaction conditions, we examined *o*-phenylenediamine **1 a** and sodium hydroxy(4-methoxyphenyl)methanesulfonate **2 h** as standard substrates (Table 1). In the initial attempt, the reaction was conducted for 30 minutes, yielding the desired product **3 ah** with a 41% yield and forming **3 ah′** with a 4% yield. Increasing the reaction time to 60 minutes improved the yield to 62% (Table 1, entry 2). The best results (70%) were obtained after 1.5 hours of milling at room temperature using MeOH as a LAG (Table 1, entry 3).

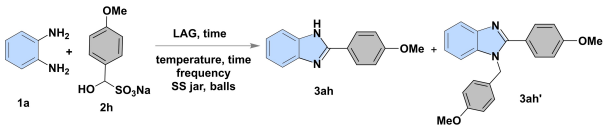
However, extending the reaction time yielded insignificant results (as shown in Table 1, entry 4). The reaction was also performed at a temperature of 70 °C, which resulted in a 64% yield of the desired product (as shown in Table 1, entry 5). Furthermore, attempting to improve the yield of the desired product **3 ah** by testing other solvents, such as acetone and ^{i}PrOH as a LAG, yielded no positive results (as shown in Table 1, entries 6 and 7). Doubling the amount of bisulfite adduct **2 h** under the standard reaction conditions also did not yield a satisfactory improvement. Furthermore, as widely reported in various solvent-based processes,[22] oxidants are typically involved alongside aldehydes,[23] but their presence was ineffective in improving yields under mechanochemical conditions (Table 1, entries 9 and 10). Remarkably, only 36% of the desired product (**3 ah**) was obtained in the absence of any solvent as a LAG, proving how it is essential the role of a stoichiometric solvent amount in achieving a good conversion rate (Table 1, entry 11).

In solution, Bertagnini's salts are in equilibrium with the aldehyde component, the active reactive species.[24] Notably, during the reaction, ^{1}H NMR analysis (Figure 3) conducted on the crude reaction revealed no signals associated with the presence of aldehyde species, proving that the whole dynamics are different under solid-state conditions.

We extensively tested our synthesized method for benzimidazole synthesis using various substituted *o*-phenylenediamines and Bertagnini's salts under the standard reaction conditions, as illustrated in Scheme 1, to demonstrate its practical applicability.

The initial reaction between unsubstituted *o*-phenylenediamines and bisulfite adducts with an electron-

Table 1. Optimization of the reaction conditions.



Entry	**2 h** (equiv.)	Solvent (η factor)	Time (min)	**3 ah** (%)[a]
1	1.1	MeOH (0.4)	30	41 (**3 ah′**:4%)[b]
2	1.1	MeOH (0.4)	60	62 (**3 ah′**:5%)[b]
3	1.1	MeOH (0.4)	90	70 (**3 ah′**:15%)[b]
4	1.1	MeOH (0.4)	120	70%
5[c]	1.1	EtOH (0.4)	90	64%
6	1.1	Acetone (0.4)	90	49%
7	1.1	^{i}PrOH (0.4)	90	47%
8	2.0	MeOH (0.4)	90	69%
9[d]	1.1	MeOH (0.4)	90	51%
10[e]	1.1	MeOH (0.4)	90	46%
11[f]	1.1	–	90	36%[b]

All the reactions, otherwise stated, were run using 0.50 mmol of *o*-phenylenediamine **1 a** with a 5 mL stainless steel jar equipped with one SS ball 7 mm Ø at 30 Hz.
[a] The conversion rate was calculated on isolated yields.
[b] Yields determined by NMR analysis.
[c] The reaction was run on a 1.0 mmol scale, and a 70 °C by using a Retsch-MM500 Control ball mill in a 4x10 mL SS jar equipped with two balls 7 mm Ø at 30 Hz.
[d] 1.00 eq of potassium periodate was added.
[e] 1.00 eq of potassium peroxymonosulfate was added.
[f] Reaction was performed without using any LAG.

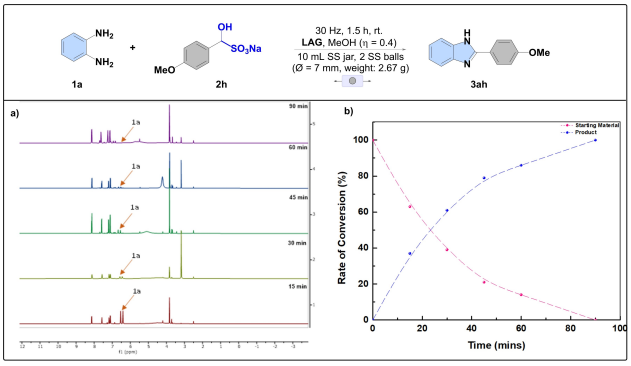
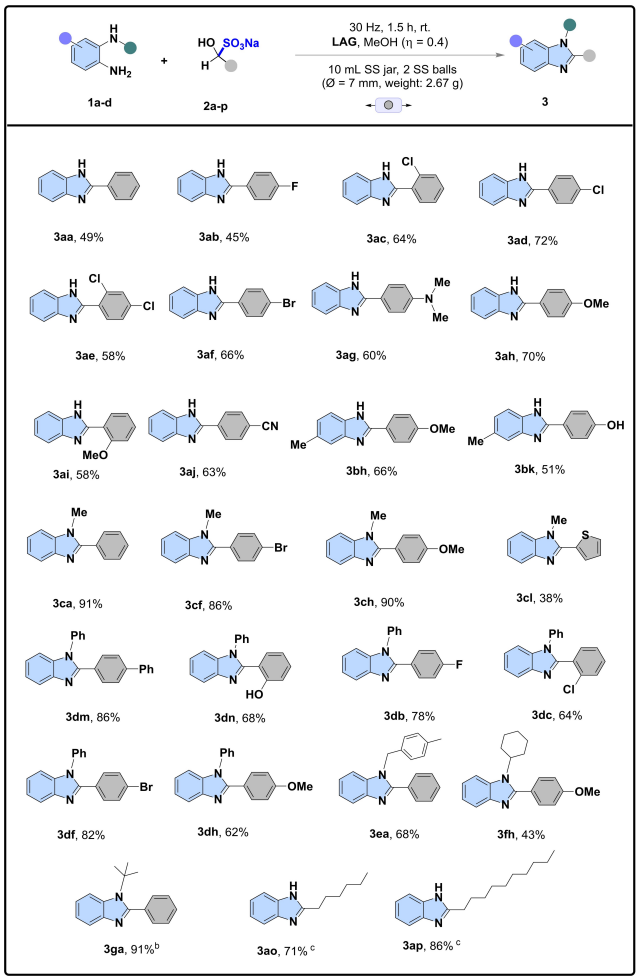


Figure 3. Reaction progress with increasing the reaction time.



Scheme 1. Reaction Scope for Benzimidazoles. Reaction conditions: o-Phenylenediamine (1 mmol) and substituted bisulfite adducts (1.1 mmol) were added in a 10 mL SS jar with two 7 mm SS balls. The reaction was performed at 30 Hz for 90 mins under room temperature conditions. Yield of the product was calculated after recrystallization with ethanol. [b]Reaction was performed using ethanol (η factor = 1.0) at 80 °C under an O_2 atmosphere in a ball mill (30 Hz) for 3 hours. [c]Reaction was performed at 15 Hz for 8 h (using methanol, η = 1) under room temperature conditions, and the product yield was calculated after column chromatography.

withdrawing group resulted in a good yield of a cyclized product **3 ab**–**3 af**. Electron-donating groups in the bisulfite adducts facilitated smooth reactions, yielding the desired products **3 ag**–**3 ai**.

Introducing a cyano substituent at the *para* position of Bertagnini's salt resulted in a 63% yield of product **3 aj**. Similarly, the incorporation of a methyl group onto the *o*-phenylenediamine ring, specifically 4-methylbenzene-1,2-diamine, in conjunction with *p*-methoxy and hydroxy-containing bisulfite adducts, produced products **3 bh** and **3 bk** with yields of 66% and 51%, respectively.

We further investigated the reactivity of Bertagnini's salts with *N*-substituted (methyl, phenyl, 4-methyl benzyl, cyclohexyl, and *tert*-butyl)-phenylenediamines (Scheme 1, compounds **3 ca**–**3 fh**). These diamine structures yielded more favorable results compared to unsubstituted o-phenylenediamines. When a thiophene-containing bisulfite adduct reacted with *N*-methyl phenylenediamine under standard conditions, it produced **3 cl** with a 38% yield.

The presence of a bulky substituent on the nitrogen of *N*-phenyl o-phenylenediamine did not hinder the synthesis of cyclized products **3 dm**–**3 dh**, obtained with moderate results. Moreover, incorporating 4-methyl benzyl and cyclohexyl groups on the nitrogen of o-phenylenediamine resulted in the desired products with good yields (**3 ea** and **3 fh**). The insertion of a *tert*-butyl group on the nitrogen of o-phenylenediamine failed to deliver the cyclized product under the standard reaction condition, which produced the condensation product (**3 gh**) (Scheme 5A).

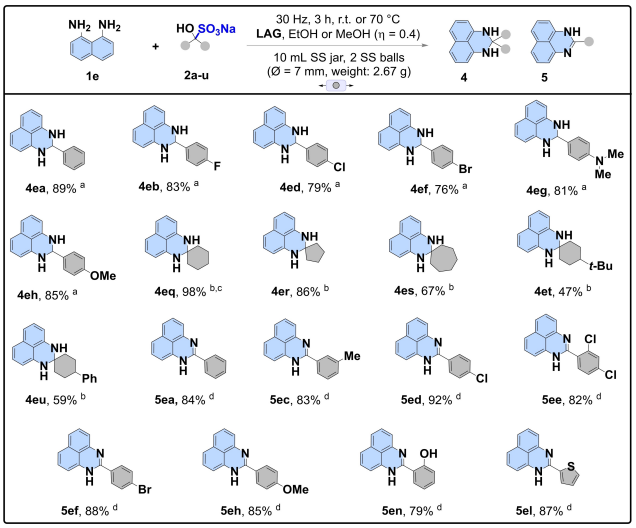
Notably, the target cyclized product **3 ga** was successfully synthesized with a high yield of 91% when the reaction was conducted using ethanol as a Liquid-Assisted Grinding (LAG) medium (η factor = 1.0) at 80 °C, under an O_2 atmosphere in a ball mill (30 Hz) for a duration of 3 hours.

While extensive research has explored 2-aryl benzimidazoles well, synthesizing 2-alkyl benzimidazoles[25] under metal-free conditions at room temperature remains to be established.

Unfortunately, we did not obtain the desired product under the optimized conditions. Working with only solid components, we can operate in the presence of small amounts of solvent (LAG), which gives us more options. We are delighted to report that we synthesized products **3 ao** and **3 ap** by running the entire process at room temperature for 8 hours under LAG conditions (η = 1).

Nitrogen-containing tricyclic heterocycles,[26] such as perimidines and 2,3-dihydro-1*H*-perimidines, are omnipresent in various natural products[27] and exhibit several biological activities,[28] photochromic properties[29] and other peculiar features commonly used in different fields.[30] Concerning the synthesis of these *N*-heterocycle scaffolds, several traditional methods were well documented in the literature,[31] but longer reaction times, high temperatures, use of hazardous solvents, expensive reagents, and lower yield of the products are the major drawbacks. Therefore, developing an efficient, environmentally friendly alternative to current approaches has become essential for resolving such traditional obstacles.

Here, we have investigated the synthesis of 2,3-dihydro-1*H*-perimidines, spiro-perimidines, and perimidines from substituted bisulfite adducts with 1,8-diaminonaphthalene under mechanochemical conditions (Scheme 2). The benzaldehyde bisulfite adduct



Scheme 2. Reaction Scope for 2,3-dihydro-1*H*-perimidines and Perimidines. Reaction conditions: 1,8-Diaminonaphthalene (1 mmol) and substituted bisulfite adducts (1.1 mmol) were added in a 10 mL SS jar with two 7 mm SS balls. [a]The reaction was performed at 30 Hz for 30 mins at rt, and yield was calculated after recrystallization with ethanol. [b]The reaction was performed at 30 Hz for 3 hrs at rt, and yield was calculated after column chromatography. [c]No column chromatography was needed. [d]The reaction was performed at 30 Hz for 3 hrs at 70 °C (using ethanol as a LAG), and the yield was calculated after recrystallization with ethanol.

reacted with 1,8-diaminonaphthalene at room temperature and yielded 89% of the cyclized product **4ea** in 30 minutes. Introducing electron-withdrawing groups (–F, -Cl, -Br) in the aromatic ring of the bisulfite adduct gave a good yield of the corresponding products (**4eb**–**4ef**). Likewise, the Bertagnini's salts with electron-donating groups (–NMe_2 and -OMe) transformed into the corresponding cyclized derivative (**4eg** and **4eh**) with 81% and 85% yield, respectively (Scheme 2).

In addition, we broadened the synthetic potential of our procedure by employing the bisulfite adducts of cyclic ketones under room-temperature mechanochemical conditions. It is worth noting that the formation of Bertagnini's salts of cyclic ketones remains unexplored in the literature. Our experiment involved the reaction of the bisulfite adduct of cyclohexanone with 1,8-diaminonaphthalene, resulting in product **4eq** with a 98% yield within 3 hours (Scheme 2). Additionally, under the standard reaction conditions, we examined Bertagnini's salts of other cyclic ketones, including cyclopentanone and cycloheptanone, yielding the desired cyclized products **4er** and **4es** with 86% and 67% yields (Scheme 2). Moreover, the bisulfite adducts of cyclohexanone, bearing *p*-tert-butyl and phenyl substituents, were well-tolerated and yielded products **4et** and **4eu** with yields of 47% and 59%, respectively (Scheme 2).

Inspired by the reported procedures, which combine milling and a heating step,[32] we further investigated the synthesis of perimidines utilizing 1,8-diaminonaphthalene and bisulfite adducts at 70 °C. Remarkably, we achieved successful results within 3 hours under mechanochemical conditions. For a detailed optimization table regarding the synthesis of perimidines, see the Supplementary Information (Supporting Information, Table 1).

During our evaluation of reaction conditions for optimization, we used 2,3-dihydro-1*H*-perimidines (**4eh**) as model substrates. We tested numerous oxidants, but none were proven to be efficacious. Instead, we opted for a one-pot synthesis method using 1,8-diaminonaphthalene and bisulfite adducts at varying temperatures. We achieved the best result (85% yield, Scheme 2) for perimidine **5eh** using one equivalent of 1,8-diaminonaphthalene and 1.1 equivalent of 4-methoxy bisulfite at 70 °C in 3 hours whom thermal stability was confirmed by the TGA analysis (Figure 1).

Using these optimal reaction conditions, we synthesized a range of perimidines by introducing different electron-donating and withdrawing groups at the bisulfite adducts moiety, resulting in moderate to excellent yields of the products (**5ea**–**5en**). Unsubstituted bisulfite adduct and 1,8-diaminonaphthalene offered efficient formation of **5ea** with 84% yield (Scheme 2). Bertagnini's salts having electron-withdrawing groups (such as Cl and Br) were efficiently converted to cyclized products (**5ed**–**5ef**) with moderate yield.

However, the methyl and hydroxyl groups of bisulfite adducts also afforded **5ec** and **5en** with 83 and 79% yield, respectively (Scheme 2). Interestingly, thiophene-containing bisulfite adducts could be transformed into corresponding perimidine (**5el**) with an 87% yield.

To showcase the versatility of Bertagnini's salts, the reactivity of other nucleophiles was analyzed. In reductive aminations, an aldehyde reacts with an amine to form a transient imine, which is then reduced to the corresponding secondary amine.[33] This method is extensively used for selectively functionalizing primary amines, thereby avoiding any potential polyalkylation event on the nitrogen moiety. In this perspective, reductive amination of bisulfite adduct with amines was achieved by 2-picoline borane as a reducing agent in methanol solvent[34] and α-picoline-borane aqueous micellar catalysis conditions at 60 °C.[9a] Despite performing, these processes involve using hazardous organic solvents, detrimental surfactants, expensive reducing agents, and precise temperatures. Moreover, combining surfactants and water can be harmful since they contaminate drinking water. If

this happens, the polluted water must be distilled to be purified, making the entire procedure unsustainable on an industrial scale.

In this regard, we have shown the reductive amination of Bertagnini's salt utilizing $NaBH_4$ as a hydride source under mechanochemical and room temperature conditions. To demonstrate the sustainability of our mechanochemical approaches, green metrics were calculated to compare the traditional procedure to our developed strategy (see the ESI file for further information). The reaction was performed in a two-step, one-pot synthesis in which the first step consists of the mechanochemical synthesis of imines within 3 hours, followed by the reduction with $NaBH_4$ for a further 3 hours.

After completing the reaction, the final reaction mixture was treated with a minimal volume of ethyl acetate, resulting in efficient recovery of the secondary amine in high yield without chromatographic purification. Achieving a 75 percent reduction in mechanochemical process costs is within reach, along with a significant improvement in the atomic economy and a decrease in the release of side product pollutants such as picoline.

Various substituted bisulfite adducts were initially verified with electron-deficient and electron-poor amines, as shown in Scheme 3. Anilines reacted with unsubstituted and *N*, *N* disubstituted bisulfite adducts, resulting in the **6 fa** and **6 fg** yielding 55 and 90%, respectively.

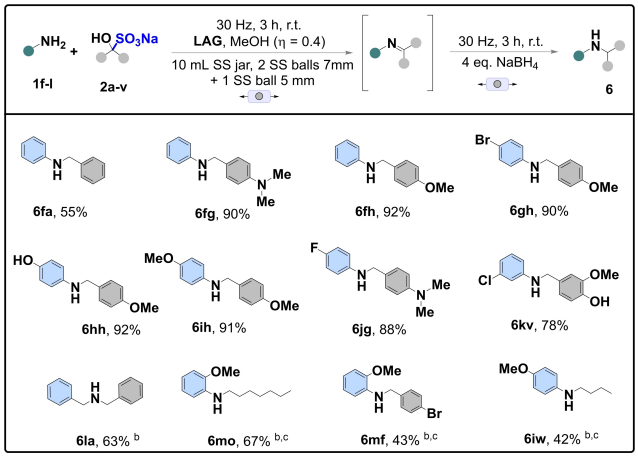
Introducing a methoxy group at the para position of the aromatic ring in bisulfite adducts, and reacting these with different anilines, led to the formation of the corresponding secondary amines (**6 fh**–**6 ih**), achieving yields ranging from 90 to 92% (Scheme 3). Further, 4-fluoro aniline could afford the desired product (**6 jg**) with an 88% yield.

Interestingly, the bisulfite adduct of vanillin also reacted with 3-chloro aniline to produce the desired product, **6 kv**, with a 78% yield. Under the standard reaction condition, benzylamine showed similar reactivity by forming the desired derivatives **6 la** in modest results. Remarkably, 2-methoxy aniline reacted with bisulfite adduct of heptanal and 4-bromo benzaldehyde to afford the desired products **6 mo** and **6 mf** with 67 and 43% yield respectively. Interestingly, the bisulfite adduct of volatile aldehyde (butyraldehyde, a VOC reagent) also coupled with 4-methoxy aniline to deliver the product **6 iw** with a 42% yield.

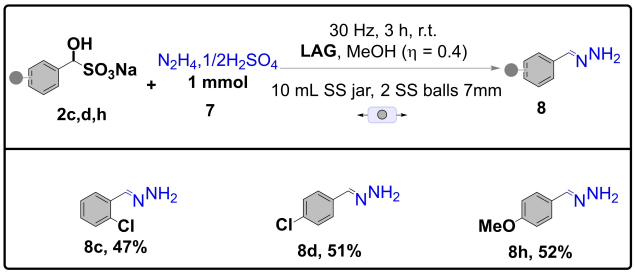
Our research has recently expanded to include the synthesis of hydrazones. This will allow us to explore the potential of Bertagnini's salt as a powerful synthetic tool, as depicted in Scheme 4. Hydrazones are a crucial structural element in countless heterocyclic scaffolds,[35] known for their various biological activities[36] in specific medical cases.[37] Using Bertagnini's salts and hydrazine hemisulfate under mechanochemical conditions allowed us to synthesize hydrazones within three hours.

This approach yielded hydrazones under mild reaction conditions and a simple purification process. The chloro-substituted bisulfite adducts afforded a remarkable 47% and 51% yield for compounds **8 c** and **8 d**, respectively. Additionally, introducing a methoxy group at the para position of bisulfites adduct resulted in a 52% yield of the corresponding hydrazone (**8 h**).

To understand the reaction progress concerning time, we have plotted a curve between the rate of conversion and reaction time (Figure 3b). The rate of conversion was calculated concerning the formation of 2-(4-methoxyphenyl)-1*H*-benzo[d]imidazole (**3 ah**) as a product, and all the product conversion rates were determined through a ^{1}H-NMR experiment. All these reactions were conducted on a 0.5 mmol scale using *o*-phenylenediamine **1 a** and sodium hydroxy(4-methoxyphenyl)methanesulfonate **2 h** as the standard sub-



Scheme 3. Reaction Scope for Reductive Aminations. Reaction conditions: Aniline (1 mmol) and substituted bisulfite adducts (1.1 mmol) were added to a 10 mL SS jar with two 7 mm SS balls and one 5 mm SS ball. [a]Reaction was performed at 30 Hz for 3 hrs, $NaBH_4$ (4 equiv.) was added to it, and the reaction was run for another 3 hrs. [b]The yield was calculated after column chromatography. [c]Reaction was performed using MeOH (η = 1) at 15 Hz for 6 hrs and 2 hrs for the reducing step.



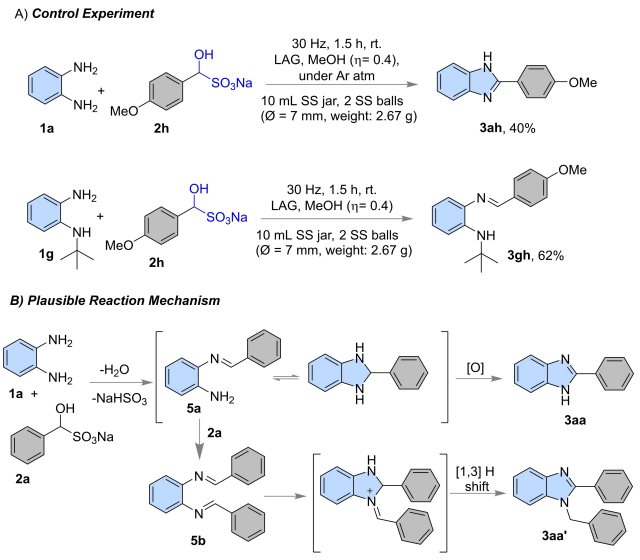
Scheme 4. Synthesis of Hydrazones.

strates. Figure 3a, states the disappearance of o-phenylenediamine **1 a** with increasing the reaction time, and all the starting materials were consumed after 90 mins.

To verify the role of oxygen in the reaction mechanism, we performed the reaction under an argon atmosphere at standard reaction conditions, which resulted in a lower yield of the expected product **3 ah** (Scheme 5A). Additionally, when the reaction was performed using a *tert*-butyl group containing *o*-phenylenediamine (**1 g**) under the standard reaction condition, the condensation imine product (**3 gh**) was isolated with 62% yield (Scheme 5A). Based on the control experiment and literature report,[38] a plausible reaction mechanism for synthesizing benzimidazoles was shown in Scheme 5B. Initially, the nucleophilic attack of amine to the carbon center of bisulfites resulted in the mono imines (**5 a**), which underwent intramolecular cyclization to generate the dihydroimidazole intermediate. Finally, the aromatized product was obtained via aerial oxidation,[16] where gaining aromaticity was the main driving force. Further, with increasing the reaction time, di-imine (**5 b**) forms, which delivered the *N*-alkylated benzimidazoles *via* the intramolecular cyclization followed by [1,3] H-shift.

Conclusion

In the past, Bertagnini salts were commonly used as reagents for removing or purifying aldehydes and ketones in reaction crudes. These solids are usually insoluble in organic solvents, and their application is also relatively less explored in organic synthesis. However, their efficacy could have been more consistent due to their insolubility in organic solvents. Bertagnini's salts have found an application in mechanochemistry as solid surrogates for aldehydes and ketones. This approach eliminates the limitations caused by their poor solubility, providing an opportunity for utilization in synthetic approaches. This study shows that Bertagnini's salts can successfully replace *liquid* carbonyl compounds in classical reactions involving aldehydes or ketones. Our strategy provides an alternative to traditional approaches that overcomes the disadvantages, such as column chromatography and workup procedure while yielding the desired products ranging from 38–91%. Additionally, we highlight the potential of this class of compounds when utilized with a mechanochemical process in the preparation of perimidine rings using thermal methods and in the proposal of the bisulfite adducts of ketones, which considerably enhanced the reactivity of this class of compounds.



Scheme 5. a) Control experiments, b) Plausible reaction mechanism.

Experimental Section

Procedure A: Synthesis of Benzimidazoles from o-phenylenediamines

A 10 mL stainless steel jar equipped with two stainless steel milling balls (7 mm diameter, 2.67 g) was filled with o-phenylenediamines **1** (1.00 mmol), bisulfite adducts **2** (1.10 mmol), and methanol ($\eta = 0.4$). The vessel was closed, and the mechanochemical reaction was conducted for 90 minutes at 30 Hz. The reaction mixture was extracted with 5 mL of methanol at the end of the reaction. Then, the extracted reaction mixture was evaporated to dryness in vacuo and purified by recrystallization with ethanol to afford the products (**3 aa- 3 dh**). However, the products **3 ao** and **3 ap** were isolated after column chromatography. In this context, the product (**3 ga**) was prepared using ethanol ($\eta = 1.0$) at 80 °C under an O_2 atmosphere in a ball mill (30 Hz) for 3 hours.

Procedure B: Synthesis of 2,3-Dihydro-1*H*-perimidines from 1,8-diaminonaphthalene

A 10 mL stainless steel jar equipped with two stainless steel milling balls (7 mm diameter, 2.67 g) was filled with 1,8-diaminonaphthalene **1 e** (1.00 mmol), bisulfite adducts 2 (1.10 mmol), and methanol ($\eta = 0.4$). The vessel was then closed, and the mechanochemical reaction was conducted for 30 min at 30 Hz. The reaction mixture was extracted with 5 mL of methanol at the end of the reaction. Then, the extracted reaction mixture was evaporated to dryness in vacuo and purified by recrystallization with ethanol to afford the products (**4 ea- 4 eh**).

Procedure C: Synthesis of Dihydro-perimidines with Cyclic Ketones

A 10 mL stainless steel jar equipped with two stainless steel milling balls (7 mm diameter, 2.67 g) was filled with 1,8-diaminonaphthalene **1 e** (1.00 mmol), bisulfite adducts **2 q–u**

(1.10 mmol), and methanol (η = 0.4). The vessel was closed, and the mechanochemical reaction was conducted for 180 minutes at 30 Hz. The reaction mixture was extracted with 5 mL of methanol at the end of the reaction. Then, the extracted reaction mixture was evaporated to dryness in vacuo and purified by silica gel column chromatography with hexane-ethyl acetate mixture to afford the expected product (**4er**–**4eu**). For the product **4eq**, the reaction mixture was extracted with 5 mL of methanol after the reaction. Then, the solvent was removed under reduced pressure to afford the pure product (**4eq**) quantitatively (No column chromatography is required).

Procedure D: Synthesis of Perimidines from 1,8-diaminonaphthalene

A 10 mL stainless steel jar equipped with two stainless steel milling balls (7 mm diameter, 2.67 g) was filled with 1,8-diaminonaphthalene **1e** (1.00 mmol), bisulfite adducts **2** (1.10 mmol), and methanol (η factor = 0.4). The vessel was then closed, and the mechanochemical reaction was conducted for 180 min at 30 Hz and 70 °C. The reaction mixture was extracted with 5 mL of methanol at the end of the reaction. Then, the extracted reaction mixture was evaporated to dryness in vacuo and purified by recrystallization with ethanol to afford the products (**5ea**- **5en**).

Procedure E: Synthesis of Amines (via $NaBH_4$ Reduction)

A 10 mL stainless steel jar equipped with 2 stainless steel milling balls (7 mm diameter, 2.67 g) and 1 stainless steel ball (5 mm diameter, 0.803 g) was filled with aniline **1f**–**m** (1.00 mmol), bisulfite adducts **2** (1.10 mmol), and methanol (η = 0.4). The vessel was then closed, and the mechanochemical reaction was conducted, ranging from 120 to 180 minutes at 30 Hz. At the end of the reaction, an additional refill of $NaBH_4$ (4.00 mmol) was made, and the mechanochemical reaction was run for 180 min at a frequency of 30 Hz. At the end of the reaction, the crude product was recovered with 4 mL of EtOAc. A further aqueous workup was made to remove the inorganic sub-products whenever necessary. Lastly, the solvent was removed under reduced pressure to afford the pure secondary amine **6**. However, the yields of products **6la**, **6mo**, **6mf**, and **6iw** were calculated after column chromatography, and the reaction was performed using MeOH (η = 1) at 15 Hz for 6 hrs and 2 hrs for the reducing step.

Procedure F: Synthesis of Hydrazones

A 10 mL stainless steel jar equipped with two stainless steel milling balls (7 mm diameter, 2.67 g) was filled with bisulfite adducts **2** (1.10 mmol), hydrazine emisulfate (1.00 mmol, 81.1 mg), and methanol (η = 0.4). The vessel was closed, and the mechanochemical reaction was conducted for 180 minutes at 30 Hz. At the end of the reaction, the crude product was recovered with 4 mL of EtOAc. Lastly, the solvent was removed under reduced pressure to afford the pure hydrazone **8**.

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