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A simple and efficient mechanochemical route for the synthesis of 2-aryl benzothiazoles and substituted benzimidazoles†

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An efficient and versatile mechanochemical route to 2-aryl benzothiazoles and both 2-substituted and 1,2-disubstituted benzimidazole derivatives has been developed *via* a simple mortar–pestle grinding method. The mechanochemical agitation was found to be sufficient for smooth condensation between a variety of aromatic aldehydes and *o*-aminothiophenol/*o*-phenylenediamine followed by cyclization leading to the formation of the corresponding 1,3-benzazoles. The salient features of this new protocol are catalyst-free reaction, cleaner reaction profiles, absence of a work-up step, high yields, and short reaction times.

1. Introduction

The development of efficient and environmentally friendly chemical processes for the synthesis of biologically active and industrially useful molecules constitutes a major challenge for chemists in organic synthesis. A sustainable and "greener" method would focus on minimal to no use of solvents, reduction of other wastes, use of ambient conditions as well as shortening of reaction time, and developing more facile ways of product separation and purification. A mechanochemical process, which typically involves the reactions induced by the input of mechanical energy such as grinding or ball-milling, facilitates most of the above mentioned features of sustainable methods and therefore, such strategies have emerged as attractive alternative to the traditional solution based synthetic methods.[1] Mechanosynthesis by "ball milling" has been used with great success for typical organic reactions[2,3] such as aldol condensation,[3a–d] Michael additions,[3e,f] Knoevenagel condensation,[3g,h] Morita–Baylis–Hillman reactions,[3i] cross-coupling reactions,[3k–o] and click reactions.[3p,q] On the other hand, manual grinding with a mortar and pestle is a very useful method at laboratory scale due to simple and hazardless experimental set-up. This technique is mostly used for condensation reactions[4] including Schiff's base formation,[4b–e] oxime formation[4f] with occasional exceptions.[5] Recently, it is found to be equally effective for the construction of heteroaromatic compounds of biological interest.[6]

Benzofused heteroaromatic compounds, in particular benzimidazoles and benzothiazoles, are common structural scaffold of biologically active compounds and natural products.[7] These heterocycles are of regular pharmaceutical interest as they show a range of pharmacological activities such as antibacterial, antiulcers, antihypertensives, antivirals, antifungals, anticancers, and antihistaminics.[8] They are an integral part of various clinical medicines as well, for example, 2-substituted benzimidazole, esomeprazole[9] is an anti-ulcerative drug, 1,2-substituted benzimidazole, astemizole is an antihistamine drug,[10] whereas, a benzothiazole derivative, Riluzole (Rilutek)[11] is used to treat motor neurone disease (Fig. 1). In addition, they are important intermediates in various organic reactions[12] and key components of many functional materials.[13] Therefore, their synthesis is a frequently encountered mission for both organic and medicinal chemists. The traditional methods for the synthesis of the benzimidazoles[14b,c] and benzothiazoles[14d] involve condensation of *o*-phenylenediamine/*o*-aminothiophenol with a carboxylic acid or its derivatives under harsh dehydrating conditions.[14] Recently, various alternative routes have been developed for these heterocycles which include transition metal catalyzed cyclization of *ortho*-haloanilides,[15] metal catalyzed direct arylation *via* C–H bond activation,[16] solid-phase supported synthesis[17] and many others.[18] However, dehydrative Schiff's base formation followed by oxidative cyclization in one-pot between *ortho*-functionalized anilines and aldehydes emerged as the most popular method for these

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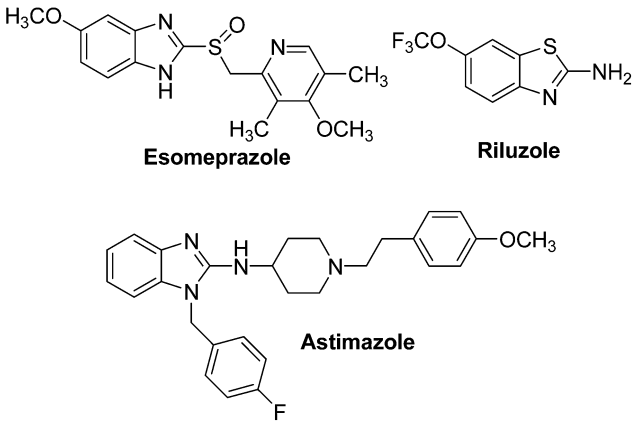
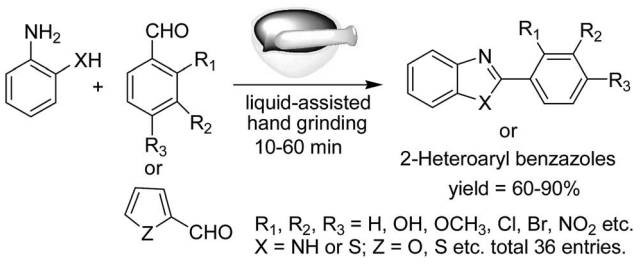


Fig. 1 Chemical structures of few 1,3-benzazole derived drug candidates.

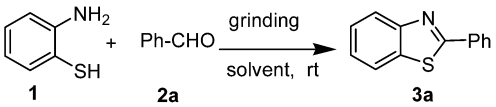
1,3-benzazole derivatives.[19–21] It is necessary to mention, majority of these methods use metal catalysts and/or additional reagents, and generate acidic and metallic wastes apart from use of considerable amounts of hazardous organic solvents for reaction and extraction processes. Therefore, their utility is limited, especially in industrial applications. In the last few years, several eco-friendly solution phase synthetic methods have been developed for both benzothiazoles[22] and benzimidazoles[22,23] by us[23a,b] and others. In many of these methods, the organic solvent is replaced by an environmentally benign solvent and reaction is often carried out in the presence of a catalyst such as surfactant. However, an eco-friendly synthesis can be turned more economical by avoiding use of catalysts, additional reagents and solvents. In this direction, we report, herein, development of an efficient mechanochemical route to 2-aryl benzothiazoles and both 2- and 1,2-disubstituted benzimidazoles (Scheme 1). The syntheses of benzimidazoles and benzothiazoles are achieved in high yields by simply grinding of a mixture of *o*-aminothiophenol/*o*-phenylenediamine and the corresponding aldehydes in an Agate mortar–pestle.

We started our work with a focus on optimizing the reaction conditions. In this direction, we first examined whether grinding under neat condition is useful or liquid assisted grinding (LAG) is more effective by keeping a model reaction between equimolar mixture of *o*-aminothiophenol (**1a**) and benzaldehyde (**2a**). The reactants were taken in an Agate mortar and ground gently with a pestle under neat condition at ambient temperature. The reaction produced a sticky solid mass after 5 min of grinding, which is partly intermediate imine and partly unreacted starting materials in addition to trace amount of desired product, as observed by TLC. As some of the unreacted starting materials were trapped inside the solid mass further reaction became sluggish under neat condition. Addition of little amount of solvent into the same reaction mixture accelerated the rate of formation of the product to a great extent. We observed that the added solvent could dissolve major part of the solid intermediates and thereby, releases trapped starting materials to facilitate their complete conversion to the desired 2-phenylbenzothiazole (**3a**). It is well-documented that liquid assisted grinding often brings out better results than "dry" grinding.[5b,24] Therefore, we used various common organic solvents for LAG and the percentage of isolated yields of the product (**3a**) was analyzed to find out the solvent of choice (Table 1). The grinding was performed up to 30 min and the progress of the reaction was monitored by TLC after each 5 min interval. In this regard, ethanol being relatively less volatile was found to be most suitable in terms of yield and rate of the reaction. The reaction goes to completion with slender amount of ethanol (0.5 mL per 1 mmol of substrate) in just 15 min (Table 1, entry 6). Whereas, only 46% of product was obtained by grinding the reaction mixture under neat condition for 30 min; rest was intermediate imine and starting materials (Table 1, entry 1). Although similar results were obtained with MeOH as solvent like EtOH (Table 1, entry 5), it was not considered for other reactions due to its higher toxicity profile. The progress of the reaction was monitored by IR spectroscopy (see ESI for details†). The IR spectra of reaction mixture were recorded at regular interval and compared with the spectra of



Scheme 1 Mechanochemical route to 2-substituted benzothiazoles and both 2- and 1,2-disubstituted benzimidazoles.

Table 1 Optimization of the reaction condition for 2-substituted benzothiazoles



Entry	Solvent	No. of equiv. of **2a**	Added oxidant	Time (min)	Yield of **3a** (%)
1	Neat	1.0	—	30	46[a]
2	CH_3Cl	1.0	—	30	68[a]
3	EtOAc	1.0	—	30	72[a]
4	CH_3CN	1.0	—	30	62[a]
5	H_2O	1.0	—	30	42[a]
6	MeOH	1.0	—	20	85
7	EtOH	1.0	—	15	88
8	EtOH	1.1	—	15	88
9	EtOH	1.2	—	15	90
10	EtOH	1.0	H_2O_2	10	85
11	EtOH	1.0	$(NH)_4S_2O_8$	15	82
12	EtOH	1.0	Iodine	15	87

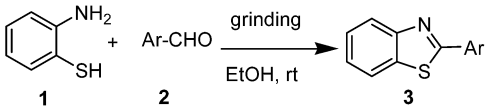
[a] Some amount starting materials and imine were also isolated.

pure starting materials and product. It was observed that the characteristic stretching bands of starting materials like carbonyl of aromatic aldehyde at 1691 cm^{-1} and amine N–H bands at 3452 cm^{-1} and 3357 cm^{-1} almost disappeared after 5 min and a sharp peak at 3388 cm^{-1} (presumably, N–H stretching band of intermediate imine) appeared in the IR spectrum due to condensation of benzaldehyde and amine group of 2-aminothiophenol to form corresponding imine. The same band significantly diminished after another 10 min indicating conversion of intermediate imine to 2-phenylbenzothiazole. In continuation of our efforts towards standardizing the reaction condition, we also examined that 1 : 1 molar ratio of *o*-aminothiophenol (**1a**) and benzaldehyde (**2a**) is ideal to achieve high yield of product (**3a**); excess aldehyde does not impose any significant improvement in the final yield (Table 1, entries 7 and 8). From the mechanistic point of view we expected that the reaction will be initiated by spontaneous formation of a Schiff's base when an aldehyde molecule comes in contact with *o*-aminothiophenol with the removal of a water molecule followed by the nucleophilic attack of sulphur atom to imine carbon to convert it to corresponding 1,2-dihydrobenzothiazole derivative, which will be finally oxidized to the desired 2-phenylbenzothiazole. Therefore, we used several nonhazardous, easily available, cheap oxidizing agents to check their effect in accelerating the aromatization step. However, added oxidizing agent had hardly any effect in terms of speed of the reaction and the yield of 2-phenylbenzothiazole (Table 1, entry 9–11). This suggests that the final oxidative aromatization step is predominantly occurred by aerial oxygen[23a] during mechanochemical agitation (Fig. 2). Therefore, we carried out rest of the reactions in minimum volume of ethanol in the absence of any added oxidizing agent.

To test the generality of this method, a series of aromatic and heteroaromatic aldehydes was treated with *o*-aminothiophenol under optimal conditions. The mortar–pestle grinding method[25] was found to be excellent in terms of yield, reaction time and cleanliness resulting in a variety of 2-substituted benzothiazoles in high yields (Table 2). The products were characterized by ^{1}H NMR, ^{13}C NMR and mass. The aldehydes with electron donating (Table 2, entries 11–14) as well as with electron withdrawing groups (Table 2, entries 2–10) participated in the reaction uniformly with no significant distinction with regard to the yields of the target products. The method was found equally suitable for heteroaromatic aldehydes (Table 2, entries 15–18). Even sensitive substrates like furfuraldehyde (Table 2, entries 15) produced the desired product in high yield. However, the variation in the substituents in the aryl ring did have influence on the rate of the reaction. Although most of the reactions were completed within 30 min, presences of strong electron donating groups in the aldehyde residue delayed complete conversion to some extent (Table 2, entry 12–14). On the other hand, aldehydes with strong electron withdrawing groups reacted faster (Table 2, entries 2, 9, 10, *etc.*), as per expectation. However, to our dismay, reaction of aliphatic aldehydes with *o*-aminothiophenol failed to produce expected results (Table 2, entries 20 and 21). As a token of demonstration, we carried out grinding of *o*-aminothiophenol with cyclohexanecarboxaldehyde and butaraldehyde. Only 10% of desired product (**3s**) was isolated after grinding the mixture up to 1 h, whereas, no product was isolated in pure form from the other reaction. Apparently, the imine was formed in due course of time but the cyclization step was retarded by the poor reactivity of the aliphatic imine group. Therefore, we restricted our study to aromatic aldehydes only.

In order to expand the scope of this method we treated *o*-phenylenediamine with various aromatic aldehydes in variable molar ratio under similar conditions, which resulted in the formation of either 2-aryl benzimidazoles or 1,2-disubstituted benzimidazoles as the major product. We observed that the

Table 2 Mechanochemical synthesis of 2-aryl benzothiazoles



1 2 3

Entry	Ar	Time (min)	Product	% Yield of **3**[a]
1	Ph	15	**3a**	88
2	4-$NO_2C_6H_4$	10	**3b**	80
3	3-$NO_2C_6H_4$	15	**3c**	83
4	4-ClC_6H_4	15	**3d**	78
5	3-ClC_6H_4	15	**3e**	81
6	2-ClC_6H_4	20	**3f**	79
7	4-BrC_6H_4	15	**3g**	81
8	3-BrC_6H_4	15	**3h**	85
9	4-FC_6H_4	10	**3i**	87
10	4-CNC_6H_4	15	**3j**	83
11	2-OHC_6H_4	60	**3k**	82
12	4-OHC_6H_4	45	**3l**	78
13	4-OH, 3-$MeOC_6H_3$	60	**3m**	78
14	4-$MeOC_6H_4$	40	**3n**	83
15	Furan-2-yl	20	**3o**	88
16	Thiophene-2-yl	20	**3p**	94
17	Indole-3-yl	20	**3q**	88
18	Pyridine-4-yl	25	**3r**	92
19	Cyclohexyl	60	**3s**	10[b]
20	Butaryl	60	—	n.d.[c]

[a] All yields refer to isolated product, characterized by ^{1}H NMR ^{13}C NMR and mass. [b] Corresponding imine was isolated as the major product. [c] No desired product was isolated and imine got decomposed during column chromatography. n.d. is not determined.

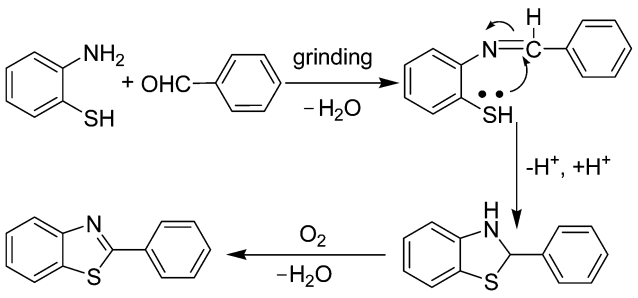
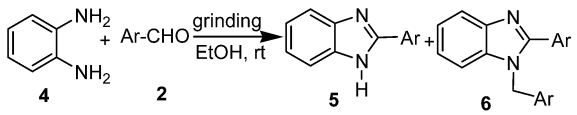


Fig. 2 Proposed mechanistic pathway for the formation of 2-phenylbenzothiazole *via* mortar–pestle grinding route.

Table 3 Mechanochemical synthesis of 2-aryl and 1,2-disubstituted benzimidazoles



Entry	Ar	Equiv. of ArCHO	Time (min)	% Yield of 2-substituted benzimidazole (**5**)[a]	% Yield of 1,2-disubstituted benzimidazole (**6**)[a]
1	Ph	1	30	62 (**5a**)	18 (**6a**)
2	Ph	2.2	30	06 (**5a**)	84 (**6a**)
3	4-$NO_2C_6H_4$	1	20	60 (**5b**)	15 (**6b**)
4	4-$NO_2C_6H_4$	2.2	30	04 (**5b**)	85 (**6b**)
5	4-ClC_6H_4	1	25	58 (**5c**)	20 (**6c**)
6	4-ClC_6H_4	2.2	30	08 (**5c**)	79 (**6c**)
7	4-BrC_6H_4	1	20	61 (**5d**)	16 (**6d**)
8	4-BrC_6H_4	2.2	30	06 (**5d**)	78 (**6d**)
9	2-OHC_6H_4	1	60	63 (**5e**)	14 (**6e**)
10	2-OHC_6H_4	2.2	60	05 (**5e**)	82 (**6e**)
11	4-$MeOC_6H_4$	1	40	66 (**5f**)	14 (**6f**)
12	4-$MeOC_6H_4$	2.2	45	07 (**5f**)	76 (**6f**)
13	Thiophene-2-yl	1	25	60 (**5g**)	16 (**6g**)
14	Thiophene-2-yl	2.2	30	04 (**5g**)	86 (**6g**)
15	Furan-2-yl	1	30	54 (**5h**)	18 (**6h**)
16	Furan-2-yl	2.2	30	05 (**5h**)	84 (**6h**)

[a] All yields refer to isolated product, characterized by melting point ^{1}H NMR ^{13}C NMR and mass.

selectivity of 2-substituted benzimidazole over 1,2-disubstituted benzimidazole is mostly dependent on the availability of the aromatic aldehyde. It was found that portion-wise addition of the aldehyde in the mortar containing *o*-phenylenediamine in ethanol with continuous grinding would lead to 2-aryl benzimidazole as the major product with 15–20% of 1,2-disubstituted benzimidazole. Whereas, addition of 1 equiv. of *o*-phenylenediamine and 2.2 equiv. of aromatic aldehydes mostly led to 1,2-disubstituted benzimidazoles with negligible amount of 2-substituted benzimidazoles making it a suitable method for the preparation of 1,2-disubstituted benzimidazoles. It is worthy to note that 2-substituted benzimidazoles can be easily separated from 1,2-disubstituted benzimidazoles by column chromatography and therefore, the same method is useful for the syntheses of 2-substituted benzimidazoles as well. Each reaction was repeated for three times and the yields of 2-substituted and 1,2-disubstituted benzimidazoles were found to be of negligible difference. The course of the reactions follows the same trend like formation of 2-aryl benzothiazoles. Substituent effect was found to be insignificant in terms of yields. However, aldehydes with strong electron withdrawing groups reacted little faster (Table 3, entry 2) and reactions were slow for aldehydes with strong electron donating groups (Table 2, entries 9–12). In general, it was observed that benzimidazole formation takes relatively longer time for completion as compared to the time required for benzothiazoles. The slight difference in reactivity may be attributed to the reduced nucleophilicity of –NH moiety as compared to sulphur atom. We also tried to synthesize benzoxazoles using mechanochemical grinding. However, couple of attempts of condensation of *o*-aminophenol with either benzaldehyde or 4-nitrobenzaldehyde followed by cyclization did not lead to desired benzoxazole derivatives. Although imine was formed, further reaction was proved to be difficult. Presumably, the oxygen atom of *o*-aminophenol is reluctant to attack newly formed imine bond due to its poor nucleophilicity under the mild reaction condition.

2. Conclusion

In conclusion, we have developed an efficient and cost effective mechanochemical route to 2-aryl benzothiazoles and both 2- and 1,2-disubstituted benzimidazoles *via* a simple mortar–pestle grinding method. A broad range of benzothiazoles and benzimidazoles have been synthesized starting from *o*-aminothiophenol or *o*-phenylenediamine and a variety of aromatic aldehydes using this method. The operational simplicity, catalyst free condition, cleaner reaction profiles, absence of work-up step, higher yields, and short reaction times make this protocol superior to many other existing methods.

Acknowledgements

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