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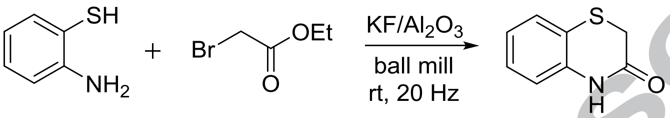

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Synergistic promoting effect of ball milling and KF-alumina support for the green synthesis of benzothiazinones

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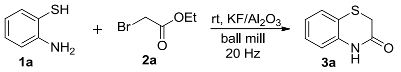
ABSTRACT

A solvent-free procedure was developed for the reaction of 2-aminothiophenols with 2-bromoalkanoates, where KF-Al_2O_3 support and ball milling cooperatively lead to a green and efficient synthesis of several benzothiazinone derivatives in good to excellent yields. The catalyst could be recycled in further reactions while maintaining its activity.

In recent decades, the implementation of environmentally green processes has gained considerable attention by synthetic chemists.[1] This strategy has led to the use of safer reagents, solvents, catalysts and energy sources,[2] and thus an overwhelming growth has been observed in the fields of solvent-free synthesis[3-5] and solid-supported reactions.[6-8] Specifically, efforts devoted to using nonconventional methods of activation have resulted in development of interesting synthetic procedures conducted under ultrasonic,[9] microwave[10] and ball milling conditions.[4,11] The latter technique, which causes mechanical grinding of solid reactants, has emerged as a rapidly growing means to conduct various synthetic transformations such as carbon−carbon couplings, carbon−heteroatom bond formation, oxidations, and reductions.[4,12,13]

On another green chemistry front, reactions catalyzed by solid-supported materials have also emerged as powerful synthetic tools in recent years.[14] In this regard, the use of potassium fluoride on alumina (KF-Al_2O_3) has become popular due to the inherently mild basic nature and characteristic properties such as enhanced reactivity and selectivity, straight forward work-up requirements and relatively mild conditions associated with this reagent.[15-18]

The benzothiazinones structural motif **3** constitutes an important class of heterocyclic compounds possessing significant pharmaceutical and biological properties.[19,20] These features have led to extensive efforts by synthetic chemists to develop efficient and simpler methods for the synthesis of these heterocycles.[21-26] Despite these accomplishments, many of the reported methods still involve more than one-step, heating at high temperatures, low yields, and demand the use of commercially unavailable starting materials or reagents. In the framework of our studies to develop environmentally benign synthetic procedures,[27] we herein report the synergistic effect from the combined use of ball milling and KF-Al_2O_3 support which promotes the solvent-free synthesis of a diverse array of benzothiazinones **3** at ambient temperature from the reaction between 2-aminobenzenethiol **1a** with ethyl 2-bromoacetate **2a** (Scheme 1).



Scheme 1

In order to determine the optimum conditions, we first examined the influence of ball milling, catalyst and reaction time (Table 1). In a typical reaction, a 1.0:1.0 mixture of **1a** and **2a** along with a 10 mm stainless steel ball were placed in a reaction vessel and the reaction mixture shaken at 20 Hz at room temperature for 30 min. When the reaction was carried out without catalyst, no product formation was observed (entry 1). In the presence of 1.0 mmol of either alumina (entry 2) or KF (entry 3), low yields of **3a** were obtained, while better results were observed when KF-Al_2O_3 was used (entry 4) indicating higher catalytic activity of the catalyst system due to good dispersion of KF over the high surface area of the alumina support. Alternatively, the same reaction without ball milling gave a lower yield of **3a** (entry 5).

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Table 1. Solvent-free synthesis of benzothiazinone **3a**.

Entry	Catalyst	Time (min)	Yield (%)[a]
1	none	30	-
2	Alumina	30	18
3	KF	30	22
4	KF/Alumina	30	40
5	KF/Alumina	30[b]	21

[a]Isolated yield.

[b]No ball milling.

The results in Table 1 showed that both the catalyst system and ball milling were necessary for the reaction. Thus, the results of entry 4 were used as the basis to further adjust the conditions so that a higher yield of **3a** would be obtained (Table 2). The use of a 20 mol% excess of **2a** dramatically increased the yield of **3a** (entry 1). The yield was further improved to 97% when the catalyst was also used in excess (entry 2), while further variations of the amounts of KF/Al_2O_3 resulted in lower conversion (entries 3-4). With no excess of **2a**, even with an increased ratio of the catalyst, reaction completion required much longer ball milling time (entries 5-9). Thus, the optimum conditions (**1a**:**2a**:catalyst = 1.0:1.2:1.5) which took a relatively short time was chosen to explore the generality of the process.

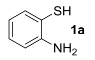
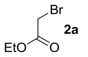
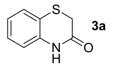
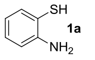
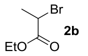
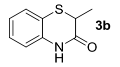
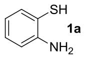
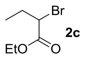
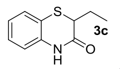
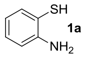
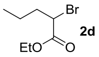
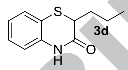
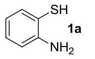
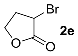
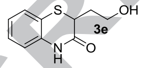
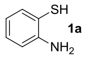
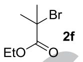
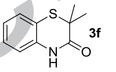
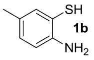
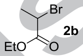
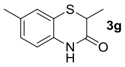
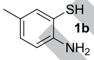
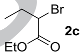
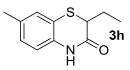
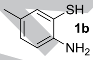
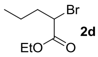
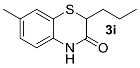
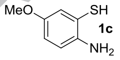
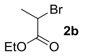
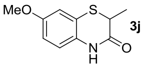
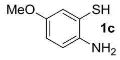
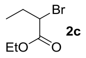
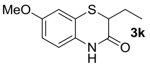
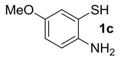
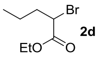
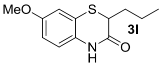
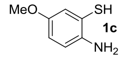
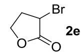
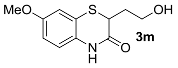
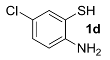
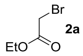
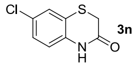
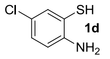
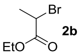
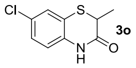
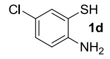
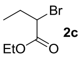
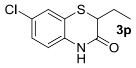
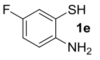
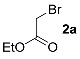
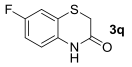
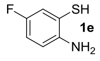
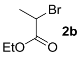
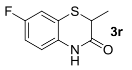
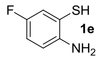
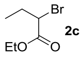
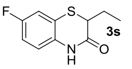
Table 2. Optimization of the solvent-free reaction conditions for the synthesis of **3a**.

Entry	**1a**:**2a**:catalyst	Time (min)	Yield (%)[a]
1	1.0:1.2:1.0	30	80
2	1.0:1.2:1.5	30	97
3	1.0:1.2:0.6	30	70
4	1.0:1.2:2.0	30	80
5	1.0:1.0:1.5	30	50
6	1.0:1.0:1.5	60	60
7	1.0:1.0:1.5	120	75
8	1.0:1.0:1.5	180	82
9	1.0:1.0:1.5	300	97

[a]Isolated yield.

Next, we evaluated the scope of the method by subjecting various derivatives of aminobenzenethiol and 2-bromoacetate to the optimized conditions (Table 3). In addition to the parent reaction (entry 1), cyclization of **1a** with various derivatives of **2** gave the desired products in 85-90% yield, where higher substituted reactants were consumed with slightly longer times (entries 2-6). The aminobenzenethiol substituted with the electron donating methyl group rapidly gave the respective products even with bulkier bromoacetates (entries 7-9). This was also the case for the reaction of the methoxy derivatives of **1** (entries 10-13). Finally, electron withdrawing substituted reactants also reacted with comparable times giving the expected products in high yields (entries 14-19).

Table 3. Expansion of the reaction scope.

Entry	Aminobenzenethiol	Bromoacetate	Product	Time (h)	Yield (%)
1	 **1a**	 **2a**	 **3a**	30	97
2	 **1a**	 **2b**	 **3b**	40	90
3	 **1a**	 **2c**	 **3c**	50	90
4	 **1a**	 **2d**	 **3d**	50	85
5	 **1a**	 **2e**	 **3e**	30	90
6	 **1a**	 **2f**	 **3f**	60	73
7	 **1b**	 **2b**	 **3g**	30	92
8	 **1b**	 **2c**	 **3h**	30	87
9	 **1b**	 **2d**	 **3i**	30	85
10	 **1c**	 **2b**	 **3j**	30	82
11	 **1c**	 **2c**	 **3k**	30	80
12	 **1c**	 **2d**	 **3l**	30	85
13	 **1c**	 **2e**	 **3m**	30	85
14	 **1d**	 **2a**	 **3n**	30	85
15	 **1d**	 **2b**	 **3o**	60	86
16	 **1d**	 **2c**	 **3p**	60	75
17	 **1e**	 **2a**	 **3q**	30	83
18	 **1e**	 **2b**	 **3r**	30	83
19	 **1e**	 **2c**	 **3s**	30	74

The reusability of the catalyst was evaluated for the reaction of **1a** with **2a**. Upon reaction completion, the reaction mixture was diluted with ethyl acetate and the suspended catalyst was filtered off. The recovered catalyst was dried and reactivated by heating in a microwave oven (360 Watt) for 5 min. The recycled KF/Al_2O_3 was used for four runs and maintained its activity in terms of yield and reaction time, only showing a gradual decrease over subsequent reactions (Figure 1).

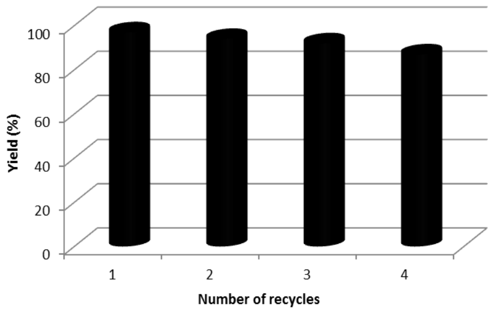


Figure 1. Reusability of the catalyst.

In summary, this work represents a useful method for the rapid synthesis of a diverse array of benzothiazinone compounds under fairly mild conditions. Some previously reported studies for the synthesis of **3a** were compared with the current method (Table 4). The present work showed very good performance in comparison to many of the previously reported studies in terms of yield, reaction conditions and time.

Table 4. Comparison of the present procedure with selected recent reported methods.

Entry	Condition	Yield% (time)
1	Et_2O, Et_3N, rt	40 (6 d)[28]
2	[Omim][NO_3], rt	98 (2 h)[29]
3	KF/Al_2O_3, IL, 85 °C,	94 (2.5 h)[30]
4	1. NaOMe/ MeOH, RX, reflux 2. Basic alumina, MW, 100 °C	71- 80 (6 min)[30]
5	NMP, DBU, MW, 180 °C	98 (4 min)[31]
6	SeO_2/dioxane, MW/ 120 °C,	82-89 (3 min)[32]
7	KF/Al_2O_3, ball mill, rt	97 (30 min)[33]

Acknowledgments

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33. *Typical procedure*: A 5.0 mL stainless steel vial was charged with a mixture of **1** (1.0 mmol), **2** (1.2 mmol), KF/Al_2O_3 (160 mg, 1.0 mmol) and a 10 mm stainless steel ball. The vial was sealed with a Teflon® gasket and the mixture was shaken at 20 Hz in an oscillatory ball mill apparatus for the appropriate length of time. After reaction completion, based on TLC, the mixture was diluted with EtOAc (10 mL) and filtered to separate the catalyst. The filtrate was concentrated under reduced pressure and if necessary, purified by column chromatography using silica gel and EtOAc/hexanes (1/10) as eluent. All products are known and their identities were confirmed by comparing their ^{1}H NMR spectra with those previously reported.[19,20,27,29,31,32]

Supplementary Material

Supplementary data (Spectra of all products) associated with this article can be found, in the online version.

Highlights

- Benzothiazinones are synthesized under solvent-free and ball mill conditions.
- Reactions take place by using inexpensive KF-Al_2O_3 support.
- The catalyst is recyclable.
- Synthesis of several derivatives show the generality and efficiency of the method.