



Environmentally benign nucleophilic substitution reactions

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ABSTRACT

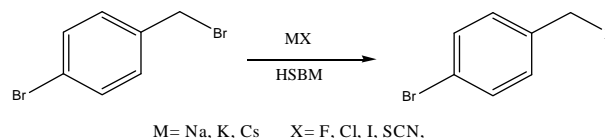
Herein, the development of environmentally benign conditions for heterogeneous nucleophilic addition reactions under novel high speed ball milling conditions is described.

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The development of environmentally benign methods to conduct chemical reactions has led to the assessment and careful analysis of reaction solvents. Although the selection of a less hazardous solvent is beneficial, the ability to conduct chemical reactions in the absence of a solvent is the best.¹ To this end, we have been studying chemical reactions using solvent-free high speed ball milling (HSBM) for a number of organic reactions. In the HSBM method, a ball bearing is placed inside a vessel that is shaken at high speeds. The high speed attained by the ball bearing has enough force to make an amorphous mixture of the reagents, which subsequently facilitates a chemical reaction.^{2–6} We look to further examine the nuances of this solvent-free technique and to apply it directly to various organic reactions. We recently demonstrated an increase in rate of the Baylis–Hillman reaction via these novel conditions.⁷ We also developed a safe solvent-free method for the reduction of esters without the use of lithium aluminum hydride.⁸ In this work, we look to focus on nucleophilic substitution reactions that traditionally use a biphasic solvent system.

Nucleophilic substitution reactions are a vital component of organic synthesis. Frequently, many of these reactions involve a non-polar organic compound and a polar ionic salt. These heterogeneous reactions are often troublesome because the polar and non-polar reagents are not soluble in a single solvent system. Phase transfer catalysts are a common auxiliary that aide these biphasic reactions. Phase transfer catalysts are responsible for billions of dollars in industrial processes; however, their use can result in lower product yields and troublesome purification issues.^{9–11} HSBM is a process that allows solids to mix in the absence of a solvent. Therefore, we wanted to investigate whether we could conduct heterogeneous reactions in the absence of a phase transfer catalyst.

In a typical fashion, *p*-bromobenzyl bromide (1.0 mmol) and the desired nucleophile (3.0 mmol) were added to a custom made 1/2" × 2" screw-capped stainless steel vial. To the vial was added



Scheme 1.

a 1/8" stainless steel ball-bearing, and the reaction mixture was ball milled in a Spex certiprep mixer/mill 5000 M for 1 h (Scheme 1). At the conclusion of the reaction, the product was washed with 10% HCl to remove the residual salt. The resulting organic solids were recrystallized in methanol and were dried via filtration. The products were analyzed by ¹H NMR, ¹³C NMR, GC–MS and were compared to literature values. The results are summarized in Table 1. We observed that potassium and sodium salts of fluoride, chloride, acetate, and cyanide did not give high yields of nucleophilic addition product under our conditions. Conversely, thiocyanate and azide provided excellent yields of the expected nucleophilic addition product.

Table 1
Various nucleophilic additions produced via Scheme 1

Entry	Metal	Nucleophile	% Conversion	% Yield
1	Na	F	—	—
2	K	F	—	—
3	Cs	F	50	50
4	Na	Cl	—	—
5	K	Cl	14	14
6	Na	I	>99	94
7	K	I	64	58
8	Na	SCN	>99	97
9	K	SCN	>99	96
10	Na	N ₃	75	75
11	Na	OAc	—	—
12	K	OAc	—	—
13	Na	CN	—	—
14	K	CN	—	—

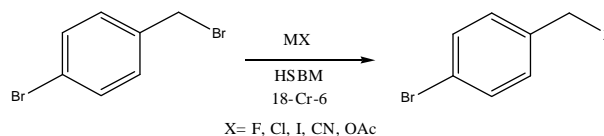
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We observed that the nucleophilicity of the anion was strongly dependent on the counter cation. Sodium and potassium fluoride did not give the corresponding *p*-bromobenzyl fluoride, but cesium fluoride provided a 50% yield of the desired product. Likewise, we noticed that potassium iodide gave much higher yield than sodium iodide, demonstrating again that the counterion is crucial under HSBM conditions.

It has been shown that with many solvent-free reactions the reagents need to create a eutectic melt in order for a reaction to occur.¹² We wanted to examine how a eutectic melt influences the product yield of the various nucleophiles. Takacs showed while milling that a Spex Mixer/Mill 5000 M reaches a global temperature of about 60 °C.¹³ Due to the fact that the melting point of *p*-bromobenzyl bromide is also about 60 °C, it is very possible that the success of these reactions is dependent on the mixture of *p*-bromobenzyl bromide and the desired nucleophile causing a phase change. When the reagents are added to the vial we do not observe a phase change; however, the reagents may reach a eutectic melt once ball milling is initiated.¹⁴ To further explore this possibility, we used a freezer mill in a liquid nitrogen environment (−196 °C) to determine if these reactions occur in low temperature conditions. We milled sodium iodide and *p*-bromobenzyl bromide for 1 h under a liquid nitrogen environment. Both ¹H NMR and GC–MS confirmed the presence of the expected *p*-bromobenzyl iodide. We also produced the nucleophilic addition product of the thiocyanate using the freezer mill; therefore, given the low temperatures that these reactions were conducted, we do not believe a phase change is a requirement for these solvent-free heterogeneous ball-milled reactions. Currently, we are in the process of exploring the effect of a phase change on the success of other ball milled organic reactions.

We thought that we could increase the nucleophilicity of the reagents through the addition of 18-crown-6 (1.0 mmol) for the potassium salt nucleophiles. The addition of 18-crown-6 led to an increase in yield and conversion for all of the potassium salt nucleophiles including those which were previously unsuccessful such as fluoride, acetate, and cyanide. 18-crown-6 is typically used as a phase transfer catalyst in solution. Therefore, we wanted to examine whether it acts as a phase transfer catalysts under our conditions. We ball milled *p*-bromobenzyl bromide and potassium chloride for 1 h with and without 18-crown-6. Both reactions produce the desired *p*-bromobenzyl chloride demonstrating that the crown ether is not a necessity for these heterogeneous reactions. The addition of the crown ether greatly increased the reaction rate;

while in the absence of 18-crown-6 the reaction needs to be milled for 48 h to achieve comparable yield.



Entry	Metal	Nucleophile	% Conversion	% Yield
1	K	F	80	80
2	K	Cl	90	90
3	K	I	70	70
4	K	OAc	>99	90
5	K	CN	>99	90

In conclusion we have demonstrated environmentally benign method for conducting heterogeneous mixtures in the absence of a phase transfer catalyst using HSBM. We look to further study HSBM in various organic reactions to further demonstrate its utility in organic synthesis.

References and notes

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- In all cases, the *p*-bromobenzyl bromide appears to have melted under the reaction conditions, while the nucleophilic salt seems to remain solid throughout the milling process. An oily-solid is present at the conclusion of all of these reactions.