Developing benign syntheses using ion pairs via solvent-free mechanochemistry

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Solvent-free mechanochemical conditions has been developed to investigate the significance of ion pairing and the use of weak bases for driving forward nucleophilic substitution reactions. This approach takes advantage of the lack of a solvent shells to incorporate weaker and safer bases to drive reactions to completion through specific ion pairing pathways. The most efficient reactions contained larger and more polarizable cation and anion pairs.

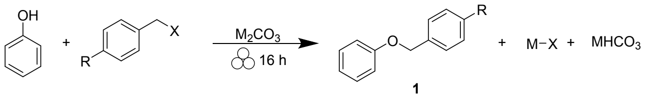
Introduction

Acid-base and nucleophilic substitution reactions are some of the most fundamental reactions in organic chemistry. Although these reactions are very reliable in the generation of new bonds, they often employ reagents and conditions that are hazardous and harmful to the environment and human health. Alkyl lithium, amides and hydrides are some of the most widely used bases in organic synthesis; however, these reagents are extremely hazardous and have been the subject of numerous incidents with some resulting in death.[1-4] We envisioned the use of solvent-free mechanochemistry as a way to suppress the use of these dangerous chemicals and substitute them for more benign reagents while achieving the desired products. Although the use of mechanochemistry has been most recognized for the ability to limit the use of harmful solvents and auxiliaries, inherently safer conditions have been demonstrated through mechanochemical conditions as well.[5-16]

In addition to the environmental impact of a solvent, solvation also suppresses the reactivity of a reagent by stabilizing it. This solvation energy needs to be overcome if a reagent is going to react in a particular reaction.[17-26] Traditionally organic chemists try to navigate this by the select use of one solvent over another (e.g. non-polar, polar protic, polar aprotic). There is a delicate balance that must be considered when choosing a solvent for this type of reaction, however the environmental effects of the solvent or safety of the reagents is often not one of them. Under solvent-free mechanochemical conditions we envisioned two benefits in the creation of more sustainable reactions of this type. First, the reaction would be conducted under solvent free conditions, significantly reducing the impact the solvent has on the environment. Second, due to the lack of solvent, there would be no solvation energy that would need to be overcome, allowing for a greater reactivity of the reagents than is observed in solution. This would in turn allow bases and nucleophiles to be stronger under mechanochemical conditions than solution allowing for the ability to generate safer reaction conditions.[26] This allows the mechanochemist to choose less hazardous reagents while getting similar results in solution. To test this thought, we compared the deprotonation and subsequent nucleophilic addition of phenols and alcohols to various electrophiles to determine whether mechanochemical conditions would allow for the use of safer nucleophilic substitution reactions than conducted solution.

Results and Discussion

One of our goals for this project was to determine how far we can take benign bases for effective use in deprotonation of certain acids. Since various carbonates have been shown to be suitable bases for phenol deprotonation in solution, the interaction between the phenoxide and the various alkali metal interactions were the first studied variables.[27-30] Metal phenoxides were synthesized to perform as nucleophiles to substitute various benzyl halides, as shown in **Scheme 1**. (M= alkali metal, X=halogen)



Scheme 1. Typical reaction scheme for the nucleophilic substitution of phenol towards various benzyl halides.

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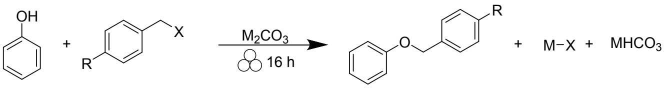
We believe there are two crucial interactions that drive this solventless reaction, both of which focus on the metal cation of the base (i.e. "M"). The first is the metal-oxygen interaction (i.e. "M—O" interaction) of the carbonate, where the weaker the ionic bond, the more likely it will want to coordinate with the halogen. The second is the metal-halogen interaction (i.e. the "M—X" interaction), where the stronger the "M—X" ion pair, the stronger the coordination to the alkyl halide. If "M—X" ion pair is strong and the "M—O" ion pair is weak, the proposed intermediate is expected to form, followed by a break down to the subsequent bicarbonate base, a metal-halogen salt, and the desired product. The reactions were tracked by both ^{1}H NMR and GC-MS to confirm product formation. Percent conversion and yield are shown in Table 1. We attempted to use bicarbonates as a base source, but those reactions gave poor yields. This suggests at least one equivalent of carbonate is needed for the reaction to give appreciable yield of product.

Under mechanochemical conditions, there is a distinct trend with the alkali metals and halogens that have a large effect on the efficiency of the reaction. The trend for both the percent conversion and percent yield tend to increase as the alkali metal and halogen became larger and more polarizable in size. We observed similar results in the solventless Wittig reaction.[31] As can be seen in **Table 1**, the most effective reaction was with caesium carbonate and 4-bromobenzyl iodide showing that the larger ion interaction of caesium-iodide is the most favourable for the substitution with phenoxides. When caesium carbonate is used as the base, we observed 75-94% conversion to the ether product, suggesting caesium carbonate is a much stronger base and/or caesium phenoxide is a much stronger nucleophile under mechanochemical conditions. The trend declines to having little to no ether product with lithium carbonate as the base. Given the strength of the lithium-oxygen bond and the weak bond strength of lithium and bromine, the proposed intermediate should not be stable and thus no ether product is produced. Instead we noticed a small amount of electrophilic aromatic substitution products which have been shown to occur when phenol is reacted directly with benzyl bromide in solution.[32]

Table 1. Percent conversion and yield of the phenol and carbonate reaction.



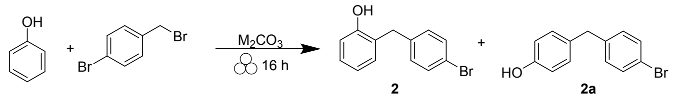
Entry	R	X	M	conversion (%)	Yield (%)[a]
1	Cl	Cl	Li	3	3
2	Cl	Cl	Na	28	10
3	Cl	Cl	K	47	44
4	Cl	Cl	Rb	62	54
5	Cl	Cl	Cs	75	72
6	Br	Br	Li	<2	<2
7	Br	Br	Na	43	38
8	Br	Br	K	69	45
9	Br	Br	Rb	79	60
10	Br	Br	Cs	87	74
11	Br	I	Li	<2	<2
12	Br	I	Na	55	49
13	Br	I	K	77	68
14	Br	I	Rb	83	78
15	Br	I	Cs	94	89

[a] Isolated yields

Upon further investigation, the ortho and para substituted electrophilic aromatic products were observed in most of the reactions as seen in **Table 2**. The ratio of products always favoured ortho, which also increased in percent conversion as the metal ion sized decreased. This demonstrates that the smaller the metal ion, the stronger it pairs with the oxygen of the carbonate and the less it will participate in the nucleophilic substitution reaction. Lithium carbonate was observed to be a weak base, producing only electrophilic aromatic substitution products, where potassium, rubidium and caesium carbonate produced smaller amounts of the aromatic substitution and more of the nucleophilic substitution. Using Pearson's Hard Soft Acid Base[33] and Jones-Dole[34] theories, it is suggestable that there should be strong overlap between lithium and oxygen making for a more stable pair, and little overlap between caesium and oxygen making this a less stable pair. This would suggest that the more stable lithium carbonate would be less reactive and give lower product yields than caesium carbonate, which is consistent with our data. In solution all reagents gave similar conversions and yields, suggesting this enhancement is unique to solvent-free conditions. Furthermore, it demonstrates the fact that the solvation negates the ability to create destabilized ion pairs due to the solvation of the nucleophiles.

Table 2. Electrophilic aromatic substitution ortho:para product

ratios and percent conversions with 4-bromobenzyl bromide and different metal carbonates.



Entry	M	conversion (**2**)	conversion (**2a**)
1	Li	22	3
2	Na	14	7
3	K	8	3
4	Rb	6	3
5	Cs	2	0

These results can be both qualitatively and quantitatively be justified using Hard Soft Acid Base Theory and/or the Jones-Dole Viscosity *B* coefficients (Table 3). For both theories, ions that have similar *B* coefficients (Jones-Dole) and have similar hardness or softness (Pearson) tend to be better paired together. This trend is illustrated with the favourability of the ion pairing of the larger ions of caesium, iodide and bromide. We can also use the ionic radius as a reference to understand the crystal structures of the MX salts in solid state and the potential overlap of certain ion pairs.[35]

In order to determine if our results are unique to para-substituted benzyl halides, we replaced the para-substituted bromobenzyl halides for ortho and meta-substituted bromobenzyl halides. We noticed the same trend with these experiments, whereby Li_2CO_3 producing little to no product and Cs_2CO_3 producing 80-92% conversion to product. Because of these results, we do not believe the halide on the aromatic ring has much effect on the overall reaction.

We propose the reaction to go through a Zimmerman-Traxler type model, where a six-membered transition state can be formed(Figure 1).[36, 37] These pathways are well known in organic synthesis and our results support at least a similar pathway.

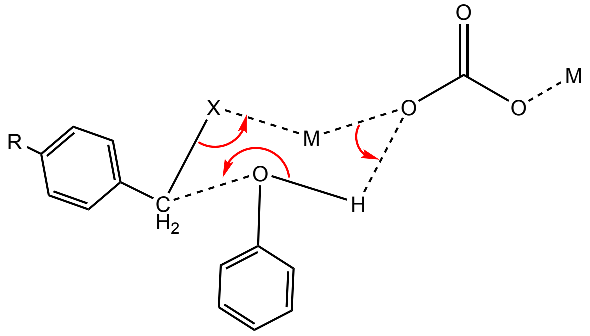


Figure 1. A proposed Zimmerman-Traxler reaction mechanism of solventless nucleophilic reaction under mechanochemical conditions.

Table 3. Pearson hardness rating and Jones-Dole Viscosity *B* coefficient

ion	HSAB Theory	Jones-Dole Viscosity B	Ionic radius (Å)
Li	Hard	0.150	0.68
Na	Hard	0.086	0.98
K	Hard	-0.007	1.33
Rb	Borderline	-0.030	1.48
Cs	Soft	-0.045	1.67
Cl	Hard	-0.007	1.81
Br	Borderline	-0.032	1.96
I	Soft	-0.068	2.19

In order to further demonstrate the ability to increase the reactivity of bases and nucleophiles under mechanochemical conditions, we reacted carbonates with a benzyl alcohol instead of phenol (**Scheme 2)**. In solution carbonates are strong enough bases to deprotonate phenols, however they are not as effective at deprotonating alcohols. Typically, much stronger, harsher reagents such as sodium hydride are used for that purpose.[38, 39] Given our success using caesium carbonate, we wanted to determine if it could be used to successful deprotonate alcohols, our results are in **Table 4**. Due to availability, ease of use, and relative small effect halogens had on the reaction, 4-bromobenzyl bromide was the only alkyl halide used for further studies.

Scheme 2. Typical reaction scheme for the nucleophilic substitution of 4-bromobenzyl alcohol towards various benzyl halides.

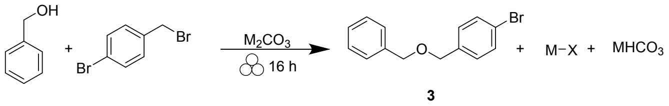
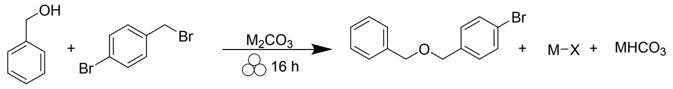


Table 4. Comparison of 1 mmol and 2 mmol of carbonate base used in substitution reaction



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Entry	M	equivalents of base	Yield (%)[a]
1	Li	1	5
2	Na	1	8
3	K	1	13
4	Rb	1	34
5	Cs	1	54
6	Li	2	5
7	Na	2	8
8	K	2	55
9	Rb	2	76
10	Cs	2	94

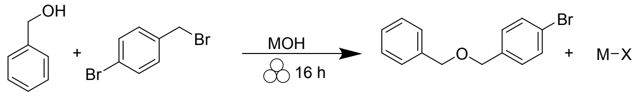
[a] Isolated yields

The efficiency of the carbonate's deprotonation was measured based on conversion and yield of the 4-bromobenzyl ether product. A similar trend to the phenol experiments was shown with the percent conversion and yield increasing as the alkali metal size increased. While this trend was similar, the success of deprotonation had decreased by approximately 20 percent with 1 equivalent of carbonate. Experiments with lithium carbonate and sodium carbonate again revealed not as much product, suggesting increased reactivity of caesium carbonate over sodium and lithium carbonates.

To see if we could increase the reactivity of carbonates with the benzyl alcohol, we increased to 2 equivalents of carbonates. We noticed a significant increase in both percent yield and conversion for all the metal cations except for lithium and sodium. Again, we believe this is due to the strong attraction these metals have with the oxygen of the carbonate. We propose a similar 6-membered transition state to the phenol reactions where the metal-oxygen and the metal-bromide reactions are important to the production of product. We believe increasing the equivalents of carbonate, increases the number of interactions between the alcohol and halide, thus increasing the amount of product.

Since we observed the efficiency of carbonates as bases, we wanted to continue to explore the use of safer bases and determine their effectiveness under mechanochemical conditions. Although hydroxides are slightly more hazardous than carbonates, they are widely used at various levels of chemistry and are easily handled by undergraduate chemists. We began these experiments with the benzyl alcohol as the acid, but used 1 mmol of hydroxides in place of carbonates. Unlike the case with carbonates, all the hydroxides produced significant yields of the desired ether **(Table 5).** Even lithium, which gave poor results for lithium carbonate, gave 52% conversion to product when lithium hydroxide was used as the base. However, when caesium hydroxide was used the reaction gave quantitative conversion and produced the highest yield. These results show that similar to solution, hydroxide acts as a stronger base/nucleophile than carbonates, however unlike solution, we can increase the reactivity of reagent through the use of proper pairing under mechanochemical conditions.

Table 5. Percent conversion and yield of substitution of 4-bromobenzyl bromide and 4-bromobenzyl alcohol
with different metal hydroxides.



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Entry	M	conversion (%)	Yield(%)
1	Li	52	36
2	Na	84	64
3	K	91	80
4	Cs	99	88

Conclusions

In conclusion, we have determined the lack of solvent stabilization affords the opportunity to use safer reagents than what could typically be used in solution. This creates an overall safer reaction pathway while still affording high yields of products. The most reactive bases were observed when there was little overlap between the ions according to either the Pearson or the Dole-Jones scale. With respect to nucleophilic reactions, we observed in addition to the nucleophile having little overlap between the ions, the metal of the nucleophile needed to have strong overlap with the leaving group of the electrophile. Finally, we were able to develop more environmentally benign conditions under mechanochemical conditions than can be observed in solution.

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