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Making kinetic and thermodynamic enolates *via* solvent-free high speed ball milling†

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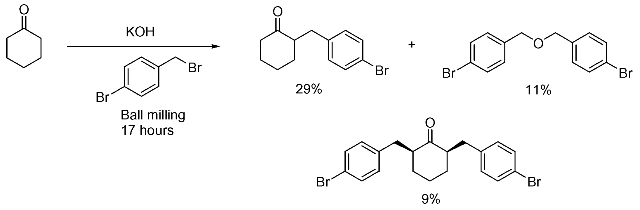
We investigated the ability to selectively form products arising from a kinetic or a thermodynamic enolate under solvent-free high speed ball milling conditions. Using 2-methylcyclohexanone as the substrate and sodium hydroxide or lithium hexamethyldisilazide as the base, we were able to trap the thermodynamic or kinetic enolate in high selectivity. Although all the reagents were ball milled simultaneously, we observed no products resulting from aldol condensation.

Environmental concerns about solvent-based chemistry have stimulated a renewed interest in the study of chemical reactions under solvent-free conditions.[1-3] Traditionally, solvent-free reactions has been performed using a mortar and pestle, but recently high speed ball milling (HSBM) has shown to be a more attractive option. 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, subsequently facilitating a chemical reaction.[4-6] The use of commercial ball mills have allowed these reactions to be scaled up to industrial levels, therefore understanding organic reactions using this methodology can significantly reduce solvent waste.[7-16]

We have recently become interested in studying various organic reactions using this novel method. In addition to our work,[17-20] various reports have shown solvent-free ball milling is a more environmentally benign alternative to traditional solution-based chemistry.[21-28] Here, we report on our investigation of the formation of kinetic and thermodynamic enolates using high speed ball milling.

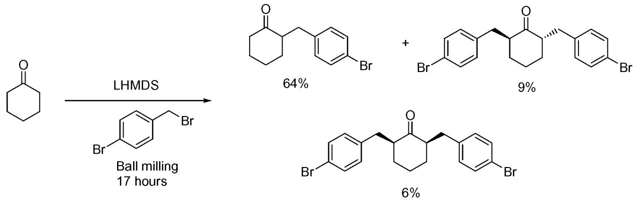
Enolates are one of the most important intermediates used for forming carbon–carbon bonds. The stereo- and regio-control of the products formed from enolates are an important aspect of organic synthesis. In solution, these reactions are conducted in a stepwise fashion whereby the base and ketone are first mixed together followed by addition of the electrophile. This is converse to the way most ball milled reactions are conducted. Typically, ball milled reactions are conducted in a sealed vessel in which all of the starting materials are added simultaneously. Creating enolates in this manner brings about the possibility of generating a complex mixture; most notably large amounts of aldol condensation products.[29] We started our study of the formation of enolates under ball milling conditions using cyclohexanone and 2-methylcyclohexanone as the substrate, *p*-bromobenzyl bromide as the electrophile, and potassium hydroxide or lithium hexamethyldisilazide as the base.

Using a custom made 1/2″ × 2″ stainless steel vial, we added cyclohexanone, *p*-bromobenzyl bromide, potassium hydroxide and a 1/8″ stainless steel ball bearing. The reaction was ball milled for an optimized time of 17 h in a Spex Certiprep Mixer/Mill 8000M. The reaction gave the monoalkylation product in 29%, the 2,6 dialkylated product in 9% (roughly 14 : 1 *cis* : *trans* ratio) and di-*p*-bromobenzyl ether in 11% yield. Under these conditions, we saw no evidence of the aldol condensation product nor did we observe the 2,2-di-*p*-bromobenzylcyclohexanone (Scheme 1).



Scheme 1 Formation of cyclohexanone enolate *via* HSBM using potassium hydroxide as base.

We next studied the formation of the cyclohexanone enolate using lithium hexamethyldisilazide (LiHMDS), a strong bulky base. We added cyclohexanone, LiHMDS and *p*-bromobenzyl bromide to a stainless steel vial with a 1/8″ stainless steel ball and ball milled as above.[30] After isolation , we observed 64% of the monoaddition product, and 15% of the 2,6-dibenzylated product (roughly 2 : 3 *cis* : *trans* ratio). Under these conditions we did not observe *p*-bromobenzyl(hexamethyldisilyl)amine which would result from nucleophilic addition of LiHMDS with *p*-bromobenzylbromide (Scheme 2). It is important to note here that we observed a switch in stereochemistry for the disubstituted product when we changed the base from KOH to LiHMDS. We



Scheme 2 Formation of cyclohexanone enolate *via* HSBM using lithium hexamethyldisilazide as base.

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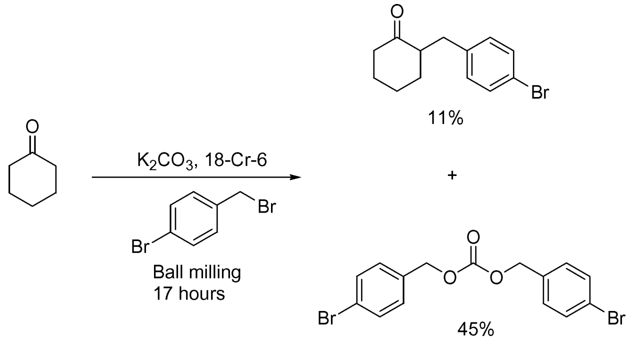
are currently investigating the nature of this stereochemical change.

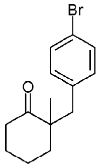
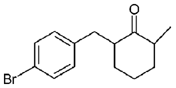
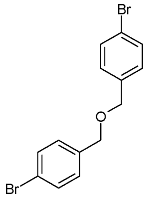
One principle of green chemistry is to use safer chemicals when possible.[31] Wang showed that bases are more reactive under solvent-free ball milling conditions than they are solution.[32] To this end, we substituted a more benign base, potassium carbonate, for LiHMDS. However, upon milling for 17 h we recovered unreacted starting materials. We added 18-crown-6 to see if that could increase the basicity; while we achieved 11% of the monoalkylation product, *p*-bromobenzyl carbonate was the major product formed in 45% yield (Scheme 3). Surprisingly, we did not observe any products resulting from aldol condensation regardless of the base that was used. However, if *p*-bromobenzylbromide is not added to the reaction mixture we form the aldol product in moderate yield; this demonstrates the preference of enolate attack towards *p*-bromobenzylbromide.



Scheme 3 Formation of cyclohexanone enolate *via* HSBM using potassium carbonate as base in the presence of 18-crown-6.

Because we obtain products resulting from formation of an enolate, we explored the possibility of preferentially forming the kinetic or thermodynamic enolate. In solution, the kinetic enolate is usually generated using low temperatures and a strong, bulky base. Conversely, the thermodynamic enolate is generated through the use of higher temperatures and a weaker base. House *et al*. showed that using lithium diisopropyl amide (LDA) with 2-methylcyclohexanone at −50 °C in 1,2-dimethoxyethane makes the kinetic enolate and upon addition of benzylbromide reacts to make 2-methyl-6-benzylcyclohexanone.[33,34] 2-Methyl-2-benzylcyclohexanone, which is made from the thermodynamic enolate, can be synthesized under similar conditions using less than 1 equivalent of LDA. Additionally, the thermodynamic enolate can be achieved by using a less hindered, equilibrating base. Artuad *et al*. showed that using potassium hydroxide in 1,2-dimethoxyethane gives the thermodynamic enolate and provides 2-methyl-2-benzyl cyclohexanone as the major product upon addition of benzyl bromide.[35] To further explore enolate chemistry in the ball mill we chose to examine the process when 2-methylcyclohexanone is used as the substrate.

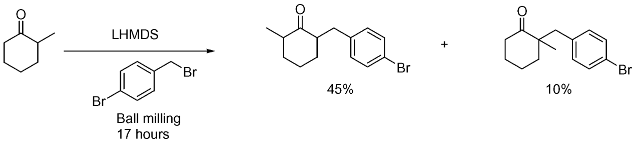
Table 1 The formation of the thermodynamic enolate as a function of the type of hydroxide used

Base			
NaOH	76%	1.8%	0%
CsF/LiOH	50%	9%	9%
KOH	29%	5%	8%
KOH[a]	9%	1%	90%
LiOH	0%	0%	0%

[a] ball milled in the presence of 18-crown-6.

In a stainless steel vial, 2-methylcyclohexanone, potassium hydroxide and *p*-bromobenzyl bromide were ball milled with a 1/8″ stainless steel ball for 17 h. In this process the thermodynamically favoured 2-methyl-2-*p*-bromobenzyl cyclohexanone was the major product but only formed in 24% yield. The product from the formation of the kinetic enolate was isolated in a 5% yield with the rest being unreacted starting material. We previously reported that the cation of the base and leaving group plays an important role in the effectiveness of the reaction under ball milling conditions.[17] Thus, we decided to explore the reaction using sodium hydroxide, lithium hydroxide and caesium hydroxide (prepared by ball milling a mixture of caesium fluoride and lithium hydroxide) (Table 1). Using lithium hydroxide as a base, we observed no reaction—only recovering unreacted starting materials. However, when we employed sodium hydroxide as the base, we were able to obtain the product resulting from formation of the thermodynamic enolate in a 76% yield. The product resulting from formation of the kinetic enolate was formed in less than 2% yield, with the rest of the mass accounted for as unreacted starting materials. We observed no dialkylation or products that resulted from aldol condensation in either of these reactions.

It has been postulated that ball milled reactions are high energy reactions such that thermodynamics should govern the system. If this is the case, the high energetics of the process along with the high concentrations of the reagents should favour thermodynamic enolate formation. To test this theory, we ball milled 2-methylcyclohexanone, LiHMDS and *p*-bromobenzyl bromide for 17 h to determine if under ball milling conditions we would be able to obtain the product which comes from formation of the kinetic enolate. At the conclusion of the reaction, we were able to isolate 2-methyl-6-*p*-bromobenzyl cyclohexanone in a 45% yield and isolated the 2-methyl-2-*p*-bromobenzyl cyclohexanone in a 10% yield with the rest recovered as unreacted starting materials (Scheme 4). This suggests that high speed ball milling conditions can provide products that are kinetically controlled. Additionally, when less than 1 equivalent of LiHMDS or sodium hydride was used, the thermodynamic product is formed preferentially. This shows that when less than one equivalent of a strong base is used equilibration of the 2-methylcyclohexanone and resulting enolate is fast compared to nucleophilic addition into *p*-bromobenzyl bromide. However, when one equivalent of LiHMDS is used the equilibration



Scheme 4 Generation of the kinetic enolate *via* HSBM conditions.

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pathway is not available and nucleophilic addition occurs at the kinetic site. Surprisingly, when 1 equivalent of a strong base such as sodium amide or sodium hydride is used we observe a preference for formation of the thermodynamic enolate.

We wanted to determine if milling time played a large role in the selectivity that we observe. When the reactions were carried out for 15 min, 2 h and 4 h the overall yields were lower but the ratio of products were unchanged.

In conclusion, we report the first analysis of enolate chemistry under high speed ball milling conditions. We demonstrated that although ball milling is theoretically an extremely high energy process, ball milled reactions can be selective and can be driven by kinetics. We are currently investigating the stereochemical nature of the process to determine if chiral auxiliaries will add stereoselectivity under these novel reaction conditions. We have also studied other ketones such as acetophenone and pinacolone (3,3-dimethyl-2-butanone) with *p*-bromobenzylbromide and observed similar results to using cyclohexanone as the substrate. In addition, we reacted 2-methylcyclohexanone with benzyl chloride and benzyl bromide and observed the enolate product similarly to what is observed when *p*-bromobenzylbromide is used as the electrophile. We are currently undergoing a more complete substrate scope to examine the fundamental rules of the process. In addition to our more complete substrate scope we are in the process of developing a greener procedure for product isolation. Ball milling can be an excellent asset for the reduction of solvent waste and the generation of more environmentally benign reactions. However, in order to achieve these goals we must first understand the nuances of this process.

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