



# Catalyzed self-aldol reaction of valeraldehyde via a mechanochemical method

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## ABSTRACT

A novel and simple one-step method for the aluminum catalyzed self-aldol reaction of valeraldehyde is presented. This mechanochemical method utilizes high-energy ball milling to produce fresh aluminum surface in the presence of valeraldehyde as a liquid milling solution. The fresh surface created through the mechanical attrition of aluminum particles during milling is highly reactive, and serves to catalyze the self-aldol reaction of valeraldehyde to form 2-propyl-3-hydroxyl-heptanal.

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## 1. Introduction

Aldol reactions are important in organic synthesis as an effective method of carbon–carbon bond formation, and are utilized in the synthesis of many large-scale commodity chemicals. In typical methods, aldol reactions are performed in the presence of strong acids or bases [1]. Under neutral reaction conditions, metal ions can be used as catalysts or reagents [2–6]. For example, Hasni et al. recently reported the formation of the self-aldol condensation product of valeraldehyde as a by-product when the aldol condensation of cyclopentanone and valeraldehyde was performed on the amphoteric Al<sub>2</sub>O<sub>3</sub> surface [7].

It has been shown that freshly exposed metal surfaces, such as those formed through in vacuo fracture or protective-layer scribing, can be exploited to take advantage of unique surface chemistries [8–12]. A newly-created surface can be highly reactive, and if created in the presence of a reactive liquid provides sites for direct interaction between the liquid media and the material surface. As such a range of chemistries, many of which would normally require multiple process steps with aggressive reagents, can instead be performed in a simple one-step method through mechanochemistry.

High-energy ball milling (HEBM) is a mechanical process commonly used to reduce particle size in a wide range of materials. In HEBM, a material is placed into a milling vial that contains a number of small milling balls. The vial is then placed in the high-

energy ball mill, where it is shaken vigorously for periods of time ranging from minutes to hours. The milling balls collide with each other and the vial walls, trapping the target material within these collisions. The ongoing impacts and collisions of the milling balls during HEBM impart mechanical energy to the system which causes the material to fracture, thus reducing particle size and creating fresh material surface. The creation of fresh material surface during HEBM is illustrated in Fig. 1.

The fresh surface created during HEBM can be easily used to facilitate such a direct reaction between a metal and a reactive liquid. By charging the vial with a reactive liquid as an additional component, the direct reaction is allowed to proceed during the HEBM process [13].

Although this reactive mechanochemical process has been previously used to passivate semiconductor nanoparticles, it is also possible to utilize the fresh metal surface as a catalyst for a reaction within the reactive liquid. Here we present a mechanochemical method for the aluminum-catalyzed self-aldol reaction of valeraldehyde to form 2-propyl-3-hydroxyl-heptanal (Scheme 1) using high-energy ball milling (HEBM).

## 2. Experimental

### 2.1. Reaction process

A stainless steel milling vial was loaded in a glovebox under nitrogen atmosphere with approximately 1.0 g of non-spherical millimeter-sized flakes of bulk aluminum and 25 mL of valeraldehyde. Stainless steel milling balls were added to the vial, which was then sealed and placed in the high-energy ball mill. After HEBM,

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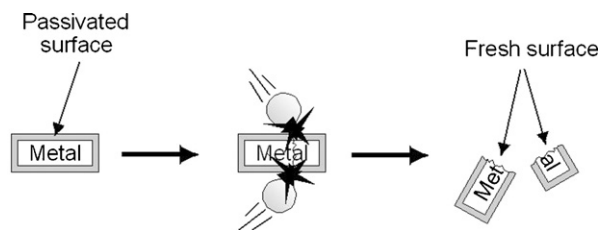


Fig. 1. Creation of fresh material surface during HEBM by material fracture.

the supernatant liquid was removed from the vial and centrifuged, removing any suspended aluminum particles.

For the control experiments, the milling vial was charged using the exact same method outlined above, save the addition of aluminum flakes to the milling vial; that is to say that valeraldehyde was the only milling component.

## 2.2. Analysis and characterization

In preparation for nuclear magnetic resonance (NMR) spectroscopy, the liquid product was removed from the milling vial and centrifuged to remove any residual aluminum particles. The liquid product was then dispersed with methylene chloride- $d_2$ . For full characterization,  $^{13}\text{C}\{^1\text{H}\}$ NMR and  $^1\text{H}$  NMR were performed, and the C–H multiplicities were determined by use of the multipulse distortionless enhancement of polarization transfer (DEPT) sequence [14]. NMR spectra were also obtained for the pure valeraldehyde reactant for comparison purposes. All NMR spectra were obtained on a Bruker Avance 300 MHz high-resolution NMR spectrometer.

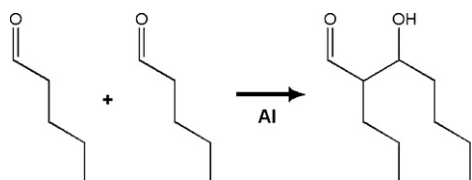
For Fourier transform infrared (FTIR) spectroscopy on the aluminum surfaces, the residual aluminum particles were isolated from the milling solution by rotary evaporation, and were redissolved in carbon disulfide. The solvent was chosen such that its own absorption peaks would not interfere with the regions of interest in the aluminum particle spectrum. FTIR spectroscopy of the milling liquid was performed using sandwiched KBr disks. All FTIR spectra were obtained at  $1\text{ cm}^{-1}$  resolution with 1000 scans using a Bruker IFS-55 spectrometer.

Gas chromatograph/mass spectroscopy (GC/MS) was performed on liquid samples using either a Varian Saturn 2100 ion trap mass spectrometer or a Varian 300 quadrupole mass spectrometer. Both instruments use electron ionization (EI). For analysis,  $1\ \mu\text{L}$  of the milling solvent was added to 1 mL of  $\text{CH}_2\text{Cl}_2$  and run at a 150:1 split ratio.

## 3. Results and discussion

### 3.1. Reaction product

Fig. 2 shows a FTIR spectrum obtained on pure valeraldehyde (top, transmittance) compared with a FTIR spectrum obtained on the liquid present after milling in the presence of aluminum for 24 h (bottom, absorbance). Although the post-milling solvent retains



Scheme 1. Self-aldol reaction of valeraldehyde to form 2-propyl-3-hydroxyheptanal.

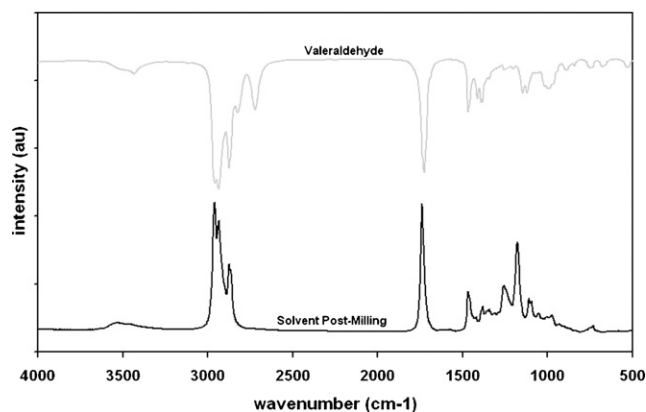


Fig. 2. Comparison of the FTIR spectrum obtained on pure valeraldehyde (top, transmittance) and the FTIR spectrum obtained on the liquid present after milling in the presence of aluminum for 24 h (bottom, absorbance).

both the distinct carbonyl peak at  $\sim 1730\text{ cm}^{-1}$  and the C–H stretching peaks from  $\sim 2800$  to  $3000\text{ cm}^{-1}$ , several differences between the two spectra can be observed. One such difference worthy to note is the evolution of the band from  $\sim 3200$  to  $3600\text{ cm}^{-1}$  belonging to –OH stretching. Also of importance is the evolution of the distinct peak at  $\sim 1174\text{ cm}^{-1}$  which is attributed to the C–OH stretching band [15]. These peaks indicate the presence of a carbon-bound hydroxyl group.

NMR spectroscopy was used to further elucidate the liquid composition and to estimate sample purity. Fig. 3 shows a  $^{13}\text{C}\{^1\text{H}\}$  NMR spectrum obtained on the liquid product after milling in the pres-

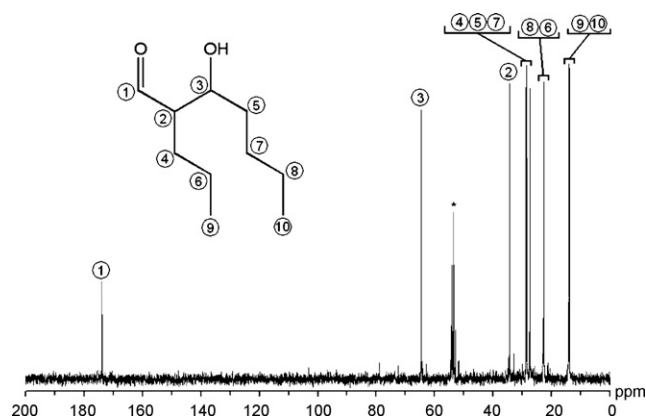


Fig. 3.  $^{13}\text{C}\{^1\text{H}\}$  spectrum of the liquid product after milling in the presence of aluminum for 24 h. Residual methylene chloride- $d_2$  peaks are denoted by an asterisk.

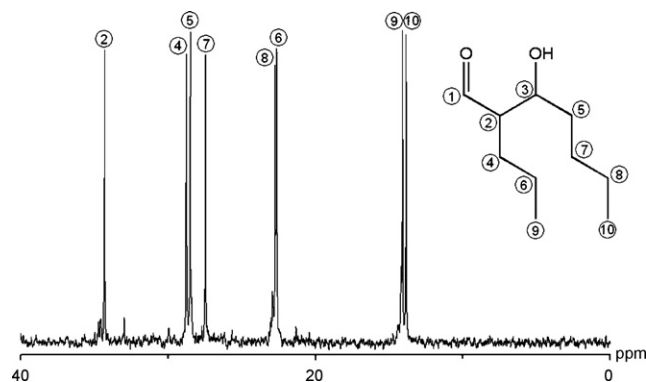
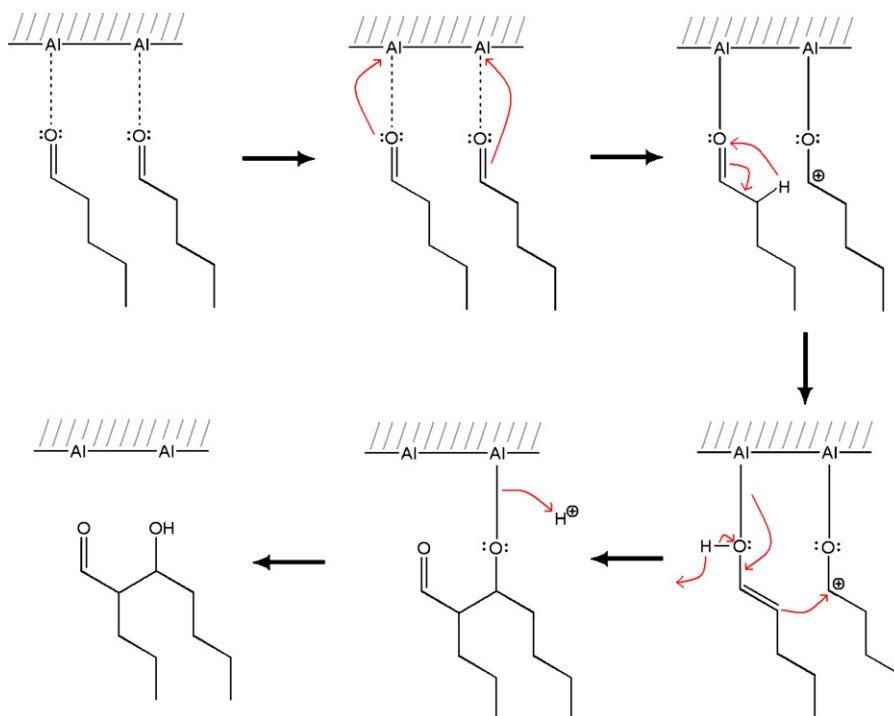


Fig. 4.  $^{13}\text{C}\{^1\text{H}\}$  spectrum of the liquid product after milling in the presence of aluminum for 24 h (same spectrum as in Fig. 3 presented with a different scale).



**Scheme 2.** Proposed mechanism for the self-aldol reaction of valeraldehyde to 2-propyl-3-hydroxyl-heptanal.

ence of aluminum for 24 h. Assignment of the  $\text{CH}_x$  multiplicities was determined by use of a DEPT sequence in a separate experiment. The NMR spectra show that two components are present in the liquid: the aldol dimer and unreacted valeraldehyde. Two new peaks at 173 ppm (carbonyl carbon) and 64 ppm (hydroxyl-bound carbon) are uniquely assigned to the self-aldol dimer. Fig. 4 is the same  $^{13}\text{C}\{^1\text{H}\}$  NMR spectrum expanded from 0 to 40 ppm. Features assignable to the self-aldol dimer include two distinct methyl resonances at 13.85 and 14.09 ppm, five methylene carbon peaks at 22.59, 22.63, 27.47, 28.49, and 28.77 ppm, and a methine peak at 34.32 ppm. Distinct peaks at 203 ppm and 43 ppm (not shown in Fig. 3) are attributed to the residual valeraldehyde. Integration of the  $^1\text{H}$  NMR spectrum shows the liquid was 67% self-aldol dimer. Ignoring any liquid products or unreacted valeraldehyde adsorbed to the sediment after centrifugation, the yield can be assumed to be roughly equivalent to the purity, or >67%. This estimate of yield was confirmed by integration of peaks in gas chromatography/mass spectrometry (GC/MS).

GC/MS was performed to further verify the molecular structure. Using an ion trap instrument, GC/MS revealed a strong high-mass peak at  $m/z = 173$ , which is the  $\text{M}+\text{H}$  peak of 2-propyl-3-hydroxyl-heptanal. This result is not unexpected since the analysis was performed on a concentrated solution where the analyte undergoes self-chemical ionization in the ion-trap, resulting in a protonated parent ion ( $\text{M}+\text{H}^+$ ). A secondary product identified from GC/MS has a parent ion of  $m/z = 154$ , which is believed to be the dehydration product of the dimer. This product was likely formed thermally in the GC column since this product was not seen in the NMR spectra. Other minor products which were identified by GC/MS include the self-aldol product of the dimer with valeraldehyde. This product was not formed in sufficient quantity to be observable in the NMR spectra.

Additionally, a control experiment was performed in which the valeraldehyde was subjected to HEBM for 24 h absent the aluminum flakes. A  $^{13}\text{C}\{^1\text{H}\}$  NMR spectrum was obtained on the liquid product after the milling process. When compared with the  $^{13}\text{C}$  NMR spectrum of valeraldehyde no substantial differences were observed,

indicating that there was no reaction. This indicates that the process of HEBM alone was not enough to induce the reaction in this system. The presence of the fresh aluminum surface created during the milling process as a catalyst is paramount to the self-aldol condensation reaction.

### 3.2. Reaction mechanism

Although the  $\text{Al}_2\text{O}_3$  surface has shown to be amphoteric in nature [7], we propose that the bare aluminum surface produced by milling will lead to an acid-catalyzed aldol reaction mechanism (Scheme 2). The fresh Al surface serves to tautomerize the carbonyl to form the enol complex, and will activate the carbonyl group of another molecule rendering it electrophilic. Being nucleophilic to the  $\alpha$ -carbon, the enol will attack the activated carbonyl compound leading to the formation of the aldol structure.

## 4. Conclusion

We have demonstrated a novel and successful method for the aluminum-catalyzed self-aldol reaction of valeraldehyde to form 2-propyl-3-hydroxyl-heptanal. Our method utilizes the fresh aluminum surface created during high-energy ball milling to facilitate a simple one-step direct reaction. The ongoing impacts and collisions of the milling balls during HEBM impart a significant amount of mechanical energy to the system which causes the aluminum flakes to fracture, thus reducing particle size and creating fresh aluminum surface. The newly created aluminum surface is highly reactive, and acts as a catalyst for the self-aldol reaction of the valeraldehyde. Furthermore, the energy input to the system by milling alone is not sufficient to allow the reaction to proceed, showing that the presence of the fresh aluminum surface plays a critical role in the reaction mechanism. The yield of this reaction under current milling conditions is >67%. A reaction mechanism has been proposed which follows the acid-catalyzed aldol reaction.

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