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mechanochemical pathway[†]

Synthesis of ketoximes via a solvent-assisted and robust

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A versatile and robust mechanochemical route to ketone-oxime conversions has been established for a broad range of ketones *via* a simple mortar-pestle grinding method. The relative reactivity of aldehydes *vs.* ketones under these conditions has also been explored, along with an examination of the possible connection between reactivity and electronic substituent effects.

Introduction

Most chemical syntheses are usually environmentally pollutive but can be made less wasteful and "greener" by minimal to no use of solvents, as well as by shortening reaction times, using ambient conditions and more facile means of product separation and purification. A mechanochemical process may be feasible for reducing waste, and such strategies have received considerable attention recently.¹ Mechanochemical synthetic processes typically involve either ball-milling or grinding, and due to their simplicity they provide an attractive alternative to the traditional solutionbased methods of chemical synthesis.²

Ketoximes comprise an important class of compounds in synthetic organic chemistry owing to their use as precursors of functional groups such as amines,³ nitriles⁴ and nitro compounds.⁵ *Via* a Beckmann rearrangement they can be converted to amides,⁶ whereas ketoxime tosylates can be converted to α -amino ketones or α -amino acetals by a Neber rearrangement.⁶ Ketoximes are also of use in the pharmaceutical industry (as organic medicinal agents such as antibiotics for the treatment of organophosphate poisoning)⁶ and as anti-skinning agents in paints and lacquers.⁷

Traditionally, ketoximes are synthesized by solution-based methods involving heating aqueous/alcoholic solutions of the ketone with hydroxylamine hydrochloride and base under reflux.^{3,8} Because of the use of organic solvents, long reaction

times and high temperatures, these methods are obviously not completely environmentally benign and thus there is a need for a less pollutive synthesis of ketoximes. An inherently greener mechanochemical path may be a better option. Ketone–oxime conversions have previously been achieved by grinding in the presence of catalysts in conjunction with microwave irradiation,⁹ by ball-milling at elevated temperatures,¹⁰ or with the aid of nanostructured pyrophosphate as a catalyst under solvent-free conditions at elevated temperatures.¹¹ Finally, the synthesis of several ketoximes has been reported *via* a simple grinding method,¹² but a more systematic investigation into the versatility of solvent-assisted mechanochemical pathways of ketone–oxime conversions, akin to what has been established for aldehyde–oxime conversions,¹³ has not yet been presented.

Herein, we report the synthesis of 20 different ketoximes decorated with a range of substituents, through solventassisted grinding of the corresponding ketone with hydroxylamine hydrochloride and sodium hydroxide under ambient conditions (Scheme 1). The products were isolated by a simple aqueous washing procedure. We have also examined the relative reactivity of aldehyde-oxime *versus* ketone-oxime conversions, and the possible electronic effects involved in such transformations.



Scheme 1 Synthesis of ketoximes via a mechanochemical route.

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Yield (%) $100^{a} (68)^{b}$

 $100^{a} (65)^{b}$

 $100^{a} (56)^{b}$

 $100^{a} (67)^{b}$

 $100^{a} (89)^{b}$

 $100^{a} (93)^{b}$

 $100^{a} (78)^{b}$

 $100^{a} (53)^{b}$

 59^b

 64^b

Results

The ketones chosen for the study were selected with the aim of determining how facile and versatile a mechanochemical process is for ketone-oxime transformations, and for identifying possible limitations of the process. Five ketones were decorated with an electron withdrawing substituent (1-5), two of them had an electron donating substituent (6 and 7), eight ketones contained structurally active functional groups such as -OH (8 and 9), -NH₂ (10 and 11) and a pyridyl group (12-15), two were multifunctionalized (16 and 17) and finally, three aliphatic ketones (18-20) were used (Table 1).

The ketoximes were synthesized by grinding the respective ketone with a mortar and pestle in the presence of hydroxylamine hydrochloride and sodium hydroxide with a few drops of methanol. The ground mixture was analysed by infrared spectroscopy (IR) to check for the disappearance of the carbonyl stretch (around 1700 cm^{-1}) in the ketone and the appearance of the -OH stretch (around $3100-3300 \text{ cm}^{-1}$) in the oxime. Following analysis by IR spectroscopy, ¹H NMR spectroscopy was used to characterize the products in the ground mixture by monitoring the -CH₃ protons. The -CH₃ protons in the ketone shift upfield by 0.3-0.5 ppm upon conversion to the corresponding ketoxime.

M.p. (°C)

134-136 (135-137)15

#	Product	M.p. (°C)
1	CI-CH3	90-93 (97-99) ¹⁴
2	Br - CH3	126–129 (128–13
3	Br N-OH	93–96 (92–93) ¹⁷
4		156–160 (156–1
5	NEC-	150-153
6	H ₃ C	81-83 (84-86) ¹⁴
7	<u> </u>	50-53 (51-52) ¹⁷

8

9

10

	Br	126–129 (128–130) ¹⁴	$100^{a} (84)^{b}$	12	N CH3	162–165 (160) ¹⁶
	Br N-OH	93-96 (92-93) ¹⁷	$100^{a} (91)^{b}$	13	⟨¬→−→ ⟨⊂H₃	114-116 (118) ¹⁶
	I-CH3	156-160 (156-158) ¹⁸	$100^{a} (78)^{b}$	14	N-OH	120–122 (119–121) ¹⁴
	NEC-	150-153	$100^{a} (72)^{b}$	15	H ₃ C-VN-OH H ₀ CH ₃	235 dec (236–238) ¹⁹
	H ₃ C	81-83 (84-86) ¹⁴	$100^{a} (71)^{b}$	16	H ₃ C HO-N HO-N	247 dec (248–250) ²⁰
	H ₃ C N-OH	50–53 (51–52) ¹⁷	$100^{a} (68)^{b}$	17	H ₃ C-V Ho	209–211 (206–208) ²¹
	но М-ОН	148–152 (148–149) ²²	$100^{a} (76)^{b}$	18	H ₃ C	_
	N-OH CH ₃	206–208 (209–210) ²²	57 ^b	19	HO_N H ₃ C	58-62 (61-62) ²³
)	N-OH	$128 - 132 (132 - 133)^{24}$	70^a	20	CH3 CH3	$127-129(128-134)^{25}$

#

11

Product

N—ОН

Yield (%)

 $100^{a} (88)^{b}$

^a % Yield calculated based on the crude ¹H NMR spectrum. ^b % Yield calculated based on the mass of the product obtained after washing the crude mixture with water. Lower yield in some cases is due to the partial solubility of the product oxime in water. Yields could be improved to 95-100% by carrying out a normal extraction. ^c Note: In a mortar, 1.0 mmol of ketone and 1.2 mmol (per ketone present) of hydroxylamine hydrochloride are ground together with a pestle. Then, 1.2 mmol (per ketone present) of crushed sodium hydroxide is added and the mixture is ground further with the addition of 0.1-0.2 mL of methanol, for 2 min at room temperature. The reaction mixture is left for 5 min, after which it is ground for another 2 min with 0.1-0.2 mL of methanol. At this stage the reaction is examined by TLC. Upon completion of the reaction, a ¹H NMR spectrum of the crude mixture is recorded in d₆ DMSO to confirm the formation of the ketoxime. The crude mixture is washed with water to remove any inorganic salts and it is air-dried, after which the melting point is determined to establish the purity of the product.

16 of the 20 reactions (1–8 and 11–18) gave complete stoichiometric conversion of the ketone to the corresponding oxime as illustrated by the ¹H NMR spectrum of the ground mixture, and no organic side products could be detected (Fig. 1). However, three reactions (9, 19 and 20) displayed an extra set of peaks in the ¹H NMR spectrum which disappeared upon washing the ground mixture with water (the correct spectrum of the corresponding pure compounds was obtained subsequently). Finally, one reaction (10) showed an incomplete conversion of the ketone to the oxime, and about 30% of the starting material remained even after doubling the ratio of hydroxylamine and base to ketone.

Discussion

Communication

The versatility and robustness of a mechanochemically-based synthetic route for ketone-oxime conversions is illustrated herein by the facile transformation of a series of aliphatic and aromatic ketones decorated with a range of substituents to their corresponding oximes. The conversion is not adversely affected by the presence of electron withdrawing, moderately electron donating, or structurally active functionalities such as -OH and pyridyl groups. Even multi-functional (16 and 17) and aliphatic reactants (18-20) can be successfully converted at ambient conditions with high yields. In a single case, that of 4-aminoacetophenone (10), we obtained a conversion of 70% to the corresponding oxime even upon increasing the ratios of hydroxylamine and base. We believe that this may be due to the strongly electron donating effect of the $-NH_2$ group at the 4-position. In the case of **11**, the $-NH_2$ group is at the 3-position and does not exert any electron donating effect as it is seen in 10; thus, 100% conversion is obtained for 11.

IR spectroscopy is a reliable and robust qualitative technique for the preliminary analysis of the ground mixtures. The disappearance of the carbonyl stretch of the ketone and the appearance of the –OH stretch of the oxime (indicative of successful transformation) is distinctive and unambiguous in all cases. A second set of peaks in the ¹H NMR spectrum of three of the reactions (**9**, **19** and **20**) is attributed to the deprotonation of the oxime in the presence of excess base. Upon washing with

Normalized Interest I

al Shift (p

Fig. 1 ¹H NMR spectrum of a ground mixture with 7.

water, the oximes become protonated again and a clean spectrum is obtained.

In order to take a close look at reaction rates and possible electronic influences, three additional competitive experiments were carried out. First, we wanted to examine the relative reactivity of aldehyde–oxime *vs.* ketone–oxime conversions (Scheme 2). Upon grinding a 1:1 mmol ratio of benzaldehyde and acetophenone with 1 mmol of hydroxylamine and base, the product ratio was 95% : 5% in favour of the aldehyde conversion, thus illustrating the greater reactivity of the aldehyde when the two functional groups are located on different molecules. This is consistent with a previous study¹⁰ which showed that competitive *ortho/para* nitrobenzaldehyde *vs. ortho/para* nitroacetophenone gave a 100% aldehyde–oxime conversion in a ball-milling reaction at room temperature. Clearly a comparable distribution of products can be achieved even by simple mortar–pestle grinding as illustrated here.

However, the situation changed slightly when an aldehyde and a ketone were located on the same backbone. When carrying out a grinding reaction of 1 mmol of 4-acetylbenzaldehyde with 1 mmol of hydroxylamine and base, the outcome was a 65%: 35% distribution in favour of the aldehyde conversion. This suggests that an electronic factor comes into play when the two functional groups are on the same backbone, and the electron withdrawing effect of the aldehyde may help to increase the reactivity of the ketone group. To test this hypothesis, we performed a competitive reaction with 1 mmol each of 4-methylacetophenone (electron donating substituent) and 4-acetylbenzonitrile (electron withdrawing substituent) in the presence of 1 mmol of hydroxylamine and base. The result was an 80% conversion of 4-acetylbenzonitrile and, consequently, a 20% transformation of 4-methylacetophenone which underscores that the electron withdrawing effect of the nitrile group on the former reactant enhances the reactivity of the ketone, thereby facilitating the ketone-oxime conversions.



Scheme 2 Relative reactivity of aldehyde *vs.* ketone (a, b) and the effect of the substituents on the reaction (c).

Conclusions

A facile, solvent-assisted and room-temperature mechanochemical synthetic pathway for the generation of ketoximes from ketones has been explored. The robustness and versatility of this simple process has been illustrated by performing the reaction on 20 different ketones with electron withdrawing (1-5), electron donating (6 and 7), structurally active groups (8-15), multifunctionalized (16 and 17) and aliphatic compounds (18-20). Several competitive experiments have shown that electronic factors (as induced by substituents on the aromatic backbone) can influence the relative reactivity. In particular, electron withdrawing substituents enhance, and electron donating groups reduce the relative reactivity of a reactant, although more work is needed to fully map out the role that such functionalities may play. The simplicity of this synthetic process, coupled with the ease of scalability and the use of environmentally benign reaction conditions make this mechanochemical route for ketone-oxime conversion a highly suitable, and environmentally less pollutive, alternative to current synthetic methodologies.

Acknowledgements

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