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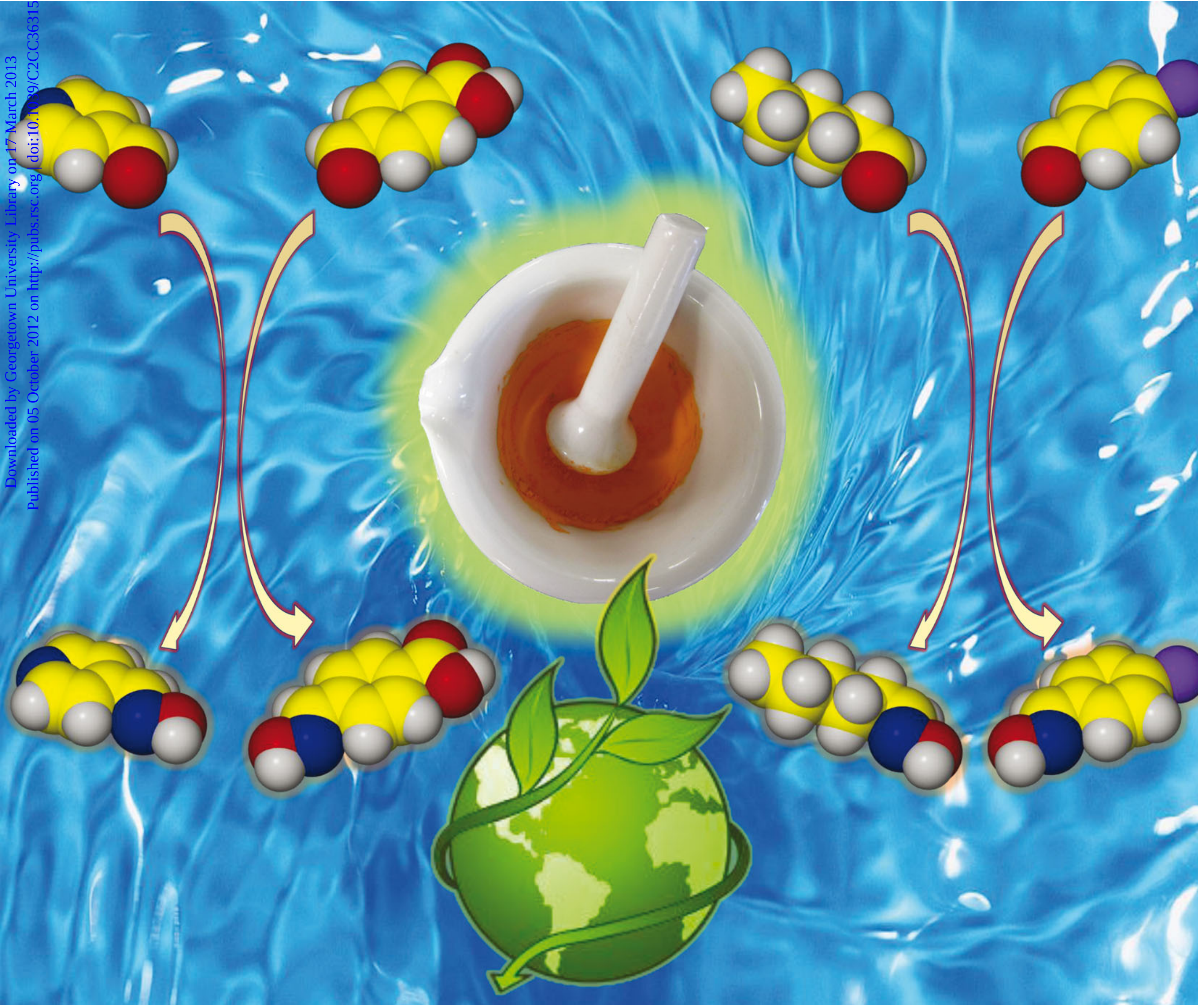

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COMMUNICATION

A versatile and green mechanochemical route for aldehyde–oxime conversions†‡

Christer B. Aakeröy,* Abhijeet S. Sinha, Kanishka N. Epa, Christine L. Spartz and John Desper

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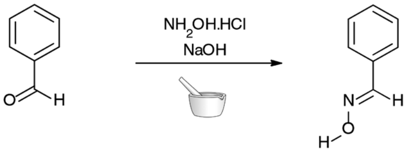
A robust, facile and solvent-free mechanochemical path for aldehyde–oxime transformations using hydroxylamine and NaOH is explored; the method is suitable for aromatic and aliphatic aldehydes decorated with a range of substituents.

Aldoximes form an important class of compounds in fundamental organic chemistry, which is employed for protection, purification[1] and characterization of aldehydes.[2] They are useful starting materials for various functional groups such as nitriles,[3] nitro compounds,[4] amines[5] and amides.[6,7] Furthermore, they can offer structure-directing capabilities in supramolecular chemistry by virtue of being strong hydrogen-bond donors (as well as being self-complementary synthons).[8] Finally, upon deprotonation, they serve as efficient ligands in the field of coordination chemistry for complexation with various metals.[9] As a result of their broad-based utility, there is a growing interest in finding better (high yielding, solvent free) and more convenient (short reaction times, easy work-up) synthetic routes.

Aldoximes are typically prepared using solution-based methods involving refluxing alcoholic/aqueous solutions of aldehyde with hydroxylamine hydrochloride and base.[2] The long reaction times, elevated temperatures, and the extensive use of organic solvents mean that these procedures are both expensive and environmentally stressful, so there is obviously a need for better options. Mechanochemistry, which is normally carried out in the absence of, or with minimal use of, solvents, could potentially offer both cheaper and greener alternatives.[10] A solid-state based mechanochemical process conforms to most of the aspects of green chemistry and thus is appealing for use in the areas of covalent synthesis and supramolecular chemistry.[11] Some advances have been made in the synthesis of aldoximes from aldehydes; for example, the use of catalysts such as $BF_3{\cdot}OEt_2$,[12] basic Al_2O_3[13] and CaO[14] have been developed in conjunction with microwave irradiated synthesis. Also, grinding in presence of Bi_2O_3[15] or ball-milling at elevated temperatures[16] has resulted in the formation of oximes in good yields, and oxime-functionalized cavitands have been prepared using solid-state grinding.[17] A previous study of carbonyl–oxime transformation included five aldehydes,[18] but no systematic investigation into the versatility of an environmentally friendly, facile, and solventless mechanochemical path to aldehyde–oxime conversions has been reported.



Scheme 1 One-pot mechanochemical conversion of aldehydes to oximes.

In this paper we present the synthesis of 20 different oximes from their corresponding aldehydes using a mechanochemical route of solvent-drop grinding in the presence of hydroxylamine hydrochloride and sodium hydroxide (Scheme 1). The grinding is done at room temperature and the reaction time ranges from 5–10 minutes. This synthetic route is green as it is essentially solvent-free, and involves short reaction times at ambient conditions. The workup of each reaction involves a simple aqueous washing procedure of the ground mixture to remove inorganic salts resulting in a pure product.

The synthetic targets were selected with a view to establishing versatility and robustness of this mechanochemical approach (Table 1). Six of the aldehydes contained electron withdrawing substituents (**1–6**), one was decorated with electron donating substituents (**7**), nine aldehydes contained structurally active functional groups such as –COOH (**8–9**), –OH (**10–13**) and pyridyl group (**14–16**), three other aldehydes were multifunctionalized (**17–19**), and finally, we also included an aliphatic aldehyde (**20**). The broad spectrum of aldehydes examined was meant to provide sufficient data to determine the limits and limitations (if any) of a solvent-free grinding for the conversion of aldehydes to oximes.

The products were characterized by ^1H NMR spectroscopy in order to establish the complete disappearance of the aldehyde proton and the emergence of the two oxime protons. In none of the 20 reactions was any evidence of an aldehyde found in the crude solid taken directly from the mortar, indicating the efficiency of the conversion (Fig. 1), and no organic side products could be detected. The work-up needed

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Department of Chemistry, Kansas State University, Manhattan, KS 66506, USA. E-mail: aakeröy@ksu.edu

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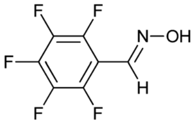
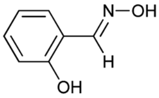
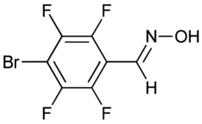
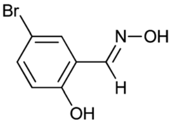
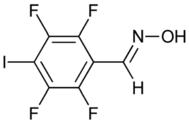
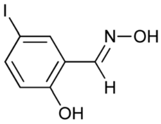
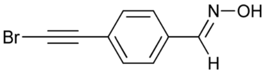
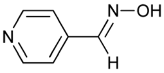
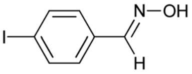
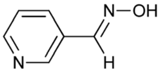
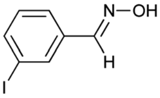
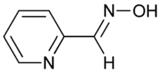
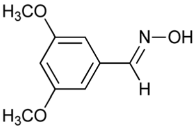
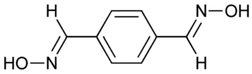
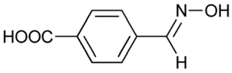
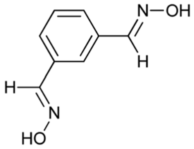
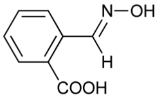
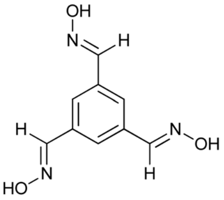
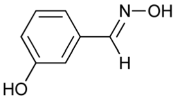
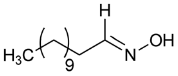
‡ Electronic supplementary information (ESI) available: Synthesis and characterization of all compounds, CIF file for the structure of **19**. CCDC 898798. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2cc36315a

Table 1 Series of the synthesized oximes

#	Product	M.p.^{a} (°C)	Yield %	#	Product	M.p.^{a} (°C)	Yield %
1		128–132 (133)	100^{b} (78)^{c}	**11**		110–116 (117)	71^{c}
2		138–140 dec (138 dec)	100^{b} (80)^{c}	**12**		112–114	100^{b} (83)^{c}
3		165–169	100^{b} (87)^{c}	**13**		124–126	100^{b} (76)^{c}
4		119–121	100^{b} (85)^{c}	**14**		130–132 (132)	100^{b} (83)^{c}
5		101–103	61^{c}	**15**		146–148 (150)	100^{b} (81)^{c}
6		66–68	59^{c}	**16**		110–114 (114)	65^{c}
7		112–114 (117)	100^{b} (89)^{c}	**17**		202–204 (201–202)	100^{b} (69)^{c}
8		212–216 (218)	67^{c}	**18**		180–182 (181–184)	100^{b} (67)^{c}
9		126–128 (128–130)	100^{b} (73)^{c}	**19**		239–241	100^{b} (64)^{c}
10		83–90 (87–88)	100^{b} (62)^{c}	**20**		70–72 (72)	100^{b} (77)^{c}

Note: In a mortar, 1.0 mole of aldehyde and 1.2 moles (per aldehyde present) of hydroxylamine hydrochloride is ground together with a pestle. Then, 1.2 moles (per aldehyde present) of crushed sodium hydroxide is added and the mixture is ground further with the addition of 2–4 drops of methanol, for 2 minutes at room temperature. The reaction mixture is left for 5 minutes, after which it is ground for another 2 minutes with 2–4 drops of methanol. At this stage the reaction is monitored by TLC. Upon completion of the reaction, a ^{1}H NMR of the crude mixture is taken in d$_6$ DMSO to confirm the formation of aldoxime. The crude mixture is washed with water to get rid of any inorganic salts and it is air dried, after which the melting point is taken to confirm the formation of pure product. ^{a} All references for the literature melting points of the products can be found in the ESI. ^{b} % Yield calculated based on the stoichiometric conversion of aldehyde to oxime as demonstrated by the crude ^{1}H NMR spectrum. ^{c} % Yield calculated based on the mass of product obtained after washing the crude mixture with water. Lower yield in some cases is due to loss of product during the washing procedure as some oximes are partially soluble in water. Yields could be improved to 95–100% by carrying out a normal extraction.

for removing inorganic salts involved a simple aqueous washing procedure. We were also able to grow single crystals of 1,3,5-benzenetricarboxaldehydetrioxime (Fig. 2). In 15 of the 20 reactions (**1–4**, **7**, **9–10**, **12–15**, **17–20**), we obtained perfect ^{1}H NMR data directly from the mortar. No organic side reactions took place, and the inorganic salts were easily removed through a

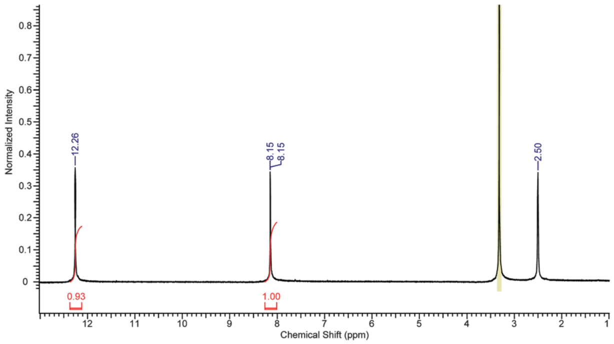


Fig. 1 ^{1}H NMR spectrum of **3** obtained from ground mixture.

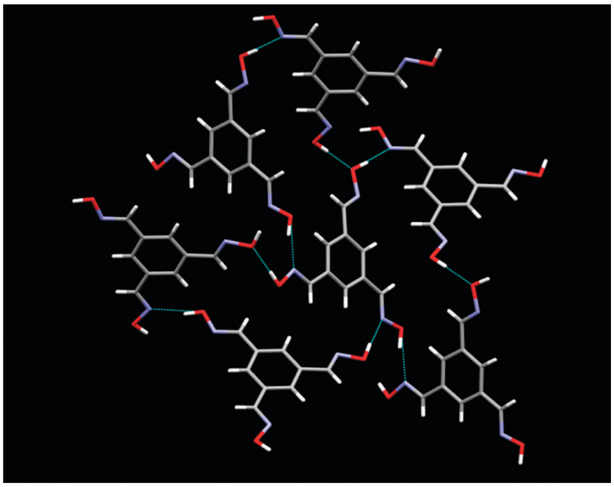


Fig. 2 Primary intermolecular interactions in the crystal structure of **19**.

simple aqueous wash. In five cases (**5**, **6**, **8**, **11** and **16**), the crude ^{1}H NMR showed an additional set of aromatic peaks which we ascertained was due to small amount of deprotonated oxime. Upon washing with water, a perfect ^{1}H NMR was again obtained in each case.

The relative efficiency of this mechanochemical approach is seemingly not influenced by the presence/absence of electron-withdrawing or electron-donating groups. Furthermore, the aldehyde–oxime conversion can also be carried out successfully using this grinding procedure even in the presence of functional groups such as –COOH, –OH, and a heterocycle (pyridine). Furthermore, the process can be carried out on multiple aldehydes simultaneously (**17–19**), as well as on aliphatic aldehydes (**20**) with no adverse effects. To further characterize the product of the reaction between hydroxylamine hydrochloride, NaOH and the 1,3,5-trisaldehyde, we were able to grow crystals suitable for single-crystal diffraction, which provided supporting evidence of the successful conversion (Fig. 2).

An examination of the crystal structure of **19** shows that two of the three hydrogen-bond donors (the –OH moieties) are engaged in O–H···N interactions with an oxime nitrogen atom (the C=N moiety) of a neighbouring molecule (O21···N23 2.804(3) Å, O21–H21···N23 1.87(4) Å), and (O25···N21 2.851(3) Å, O25–H25···N21 1.88(4) Å), respectively. The third oxime moiety forms an O–H···O interaction (O23···N25 2.799(3) Å, O23–H23···N25 1.91(4) Å) with a neighbouring molecule.

A versatile and facile mechanochemical path to aldehyde–oxime transformations has been established by examining 20 different aldehydes with different substituents such as electron withdrawing (**1–6**), electron donating (**7**), structurally active (**8–16**), multifunctionalized (**17–19**) and aliphatic (**20**) groups. The synthetic path seems to be substituent insensitive (across the range examined herein), and the ambient reaction conditions, ease of scalability, and straightforward work-up procedure make this route environmentally friendly, and a better and greener alternative to existing methods for aldoxime synthesis.

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