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Highly efficient nitrobenzene and alkyl/aryl azide reduction in stainless steel jars without catalyst addition

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The mechanochemical and selective reduction of aryl nitro and aryl/alkyl azide derivatives, with either formate salts or hydrazine, to the corresponding, synthetically useful amines occurs in excellent yields in a planetary ball mill without the addition of a catalyst. This newly developed and solvent-free protocol is efficient, fast and does not require the addition of a metal hydrogenation catalyst as the stainless steel jar itself fulfils that role. The method has been applied to a broad range of compounds and excellent yields have been obtained. The formylation of alkyl amines has been successfully performed, by means of mechanochemical activation, in the presence of ammonium formate alone.

Introduction

Green and sustainable chemistry is fast becoming a necessary requirement for both research and industry.¹ The development of new catalysts and solvent-free procedures is attracting interest from many in the organic synthesis field.² Unconventional techniques, including microwave, ultrasound, photochemical and mechanochemical procedures, have led to reductions in waste production and the consumption of solvents and energy.

Mechanochemical activation (grinding and ball milling) has not only been the object of study because it grinds and crumbles inorganic materials, but also because it generates mechanical energy for the synthesis of organic molecules.^{3,4} The planetary ball mill is a valid means of producing green energy as seen in the growth of mechanochemical activation observed in various areas of organic chemistry, including C–C bond formation,^{5–7} organocatalysis,⁸ heterocyclic synthesis,⁹ cycloaddition,¹⁰ oxidative/reductive reactions,^{11, 12} polymerisation,¹³ and supramolecular chemistry.^{14,15}

Solid–gas reactions are facilitated by mechanical milling in reactive gases (nitrogen, oxygen and hydrogen),¹⁶ and this approach was initially used for preparation of hydrides in a hydrogen atmosphere. Mechanochemistry has also seen extensive use in the hydrogen storage process, while other examples of mechanically promoted reactions performed in the presence of gaseous hydrogen have been described.¹⁷

Nevertheless, several mechanochemically activated alternatives to the use of gaseous hydrogen have been investigated: graphene oxide has been efficiently reduced in a magnesium-assisted mechanochemical reaction,¹⁸ a variety of aldehydes and ketones have been reduced to tetraalkoxyborates using unmodified sodium borohydride,¹⁹ and alkenes have been reduced using hydrogen that was generated *in situ* from alkanes.²⁰ To the best of our knowledge, only a few studies have reported the reduction of aryl nitro and aryl azide compounds in a ball mill,²¹ and none of these reactions were performed under catalyst free conditions with hydrogen generated *in situ*.

The conversion of aromatic nitro compounds and azides to amines is a fundamental procedure in organic chemistry.²² The hydrogenation of aromatic nitro compounds is one of the most relevant industrial transformations of nitro groups and the most relevant drawback of this protocol is the lack of selectivity because generally hydrogenation cannot be performed in presence of other reducible functionalities in the molecules.^{23,24} A number of heterogeneous catalytic systems have been employed for selective reduction of nitro compounds²⁵ and nanoparticles of Fe₂O₃ were discovered by Beller *et al* to provide reduction of nitro group.²⁶ On the other hand, transfer hydrogenations with HCOOH, HCOOH/TEA, HCOONH₄ and NH₂NH₂·H₂O is a convenient procedure that do not require any elaborate experimental setup of high-pressure reactors. A number of catalysts have been employed in this field with good to excellent results.²² Several investigations into the metal-free hydrogenation of nitroarenes have been published since 1995, and the most noteworthy have involved reduced graphene oxide/hydrazine hydrate, mesoporous carbon/hydrazine hydrate,^{27–29} thiourea³⁰ and glucose.³¹ Concerns about safety and environmental burden therefore make metal free hydrogenation under mechanochemical activation extremely attractive. In this work, we report the reduction of nitrobenzenes, and aryl and benzyl azides in a planetary ball

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mill, without the addition of a catalyst, in the presence of reducing agents ammonium and sodium formate, and hydrazine.

Metallic Ni, Pd and Pt have all catalysed hydrazine decomposition over various supports at low temperatures,³² while hydrazine oxidation requires high temperatures without a catalyst. Although several attempts at using hydrazine in a ball mill have been described, they are limited to the synthesis of hydrazone and the cyclization of pyrazoles.³³⁻³⁵ Hydrazine is widely used despite being toxic, therefore in the present study its reactivity has been compared with formate salts as the hydrogen source for transfer hydrogenation.³⁶⁻³⁸ Ammonium formate thermally decomposes to hydrogen, carbon dioxide and ammonia³⁹ and by contrast, the thermal decomposition of alkali metal formates, such as sodium formate, leads to carbonate, oxalate and hydrogen.^{40,41} To the best of our knowledge, no previous works have described the use of formate salts in the reduction of aryl nitro derivatives under mechanochemical activation.

Results and discussion

The reduction of nitrobenzene with hydrazine was chosen as a representative model reaction for the optimisation of reaction conditions. The decomposition of hydrazine can be performed using two methods: catalytic decomposition (on metal surfaces and supported metal particles) and thermal decomposition.⁴²⁻⁴⁴ This work presents and investigates a solvent-free method for the reduction of nitrobenzene in a planetary ball mill. A range of bases and milling auxiliaries have been tested. The amount of hydrazine was also modulated in a number of experiments. The number of balls, their size, rotation frequency and reaction time were kept constant.

As described in Table 1, the complete conversion of nitrobenzene was observed in the presence of 30 eq of hydrazine, while the reaction moved to completion and the intermediates were fully converted to aniline in the presence of grinding agent and KOH (Table 1, entry 4-7). Even if the reaction showed good conversion even in absence of grinding auxiliary,

it helps homogeneity and mixing. As in the Table 1, in presence of polar acidic basic or neutral auxiliary the reaction showed good conversion and yield, because of its chemical inertness we decided to prefer neutral alumina.⁴⁵ From the comparison of different bases, KOH was found to be the suitable one, as already observed in a previously performed mechanochemically promoted Ullmann copper-catalysed reaction.⁴⁶ The reaction rate decreased in the presence of only 20 or 10 eq of hydrazine. When performed in zirconia jar only starting material was recovered (Table 1, entry 11).

The reaction time and PM (planetary ball mill) rotation frequency (rpm, min⁻¹) were varied in order to better understand the reaction parameters (See Figure 1). The model reaction was tested at 650, 500, 400 and 200 rpm for 10 min with complete conversion being obtained at 650 rpm, which confirms that an increase in kinetic energy promoted the reduction and that higher rotational speed enhanced conversion. Milling times of 10, 20, 30 min were tested, and the complete conversion of nitro benzene to aniline was attained after 30 min.

It is known that the reaction outcome is correlated to the number of stress events and the stress frequency, therefore ball diameter and the number of balls has high impact on the reaction yields. As previously described, by mixing 5 mm and 2 mm balls we could obtain a full conversion in 30 min. In order to understand the role of 2 and 5 mm balls when used alone, the reaction was repeated as described in the table 2 (entry 2-3). The reaction gave 65 % yield with 2mm balls and it was decreased to 3% when only 5 mm ball were employed. Aimed to understand the influence of the active surface on the reaction conversion we repeated the experiment keeping constant the ball weight as in the entry 1, balls (2 and 5 mm) were used alone (Table 2, entry 4-5). We could observe that, despite the larger surface area, the reaction with 2250 small balls showed a decrease reaction yield because of the reduction of dead volume in the jar. When 144 bigger balls were used, the reaction yield was slightly reduced to 90% maybe due to a reduction of sample homogeneity in energy transferring.

Table 1. Reduction of nitrobenzene with various bases and milling auxiliaries.



Entry ^a	Auxiliary	Eq Hydrazine	Base	Ar-NH ₂ (%) ^b	Intermediate distribution ^b
1	no	30	no	89	Ar-NH-NH-Ar (4%)
2	Al ₂ O ₃ basic	30	K ₂ CO ₃	40	Ar-NH-NH-Ar (33%), Ar-N=N-Ar (15%)
3	Al ₂ O ₃ basic	30	NaOH	53	Ar-NH-NH-Ar (29%) Ar-N=N-Ar (18%)
4	Al ₂ O ₃ basic	30	KOH	99	-
5	Al ₂ O ₃ neutral	30	KOH	98	-
6	SiO ₂	30	KOH	99	-
7	Montmorillonite	30	KOH	99	-
8	Fuller Earth	30	KOH	25	Ar-NH-NH-Ar (48%), Ar-N=N-Ar (20%)
9	Al ₂ O ₃ basic	20	KOH	72	Ar-NO=N-Ar (27%)
10	Al ₂ O ₃ basic	10	KOH	77	Ar-NO ₂ (16%)
11 ^c	Al ₂ O ₃ basic	30	KOH	0	

^a Reaction conditions: nitrobenzene (4 mmol), bases (8 mmol), grinding auxiliary (1 g); 30 min, 650 rpm, stainless steel jar, 1500 balls ($\phi = 2$ mm) and 48 balls ($\phi = 5$ mm).

^b Determined by GC-MS. ^c The reaction was performed in zirconia jar

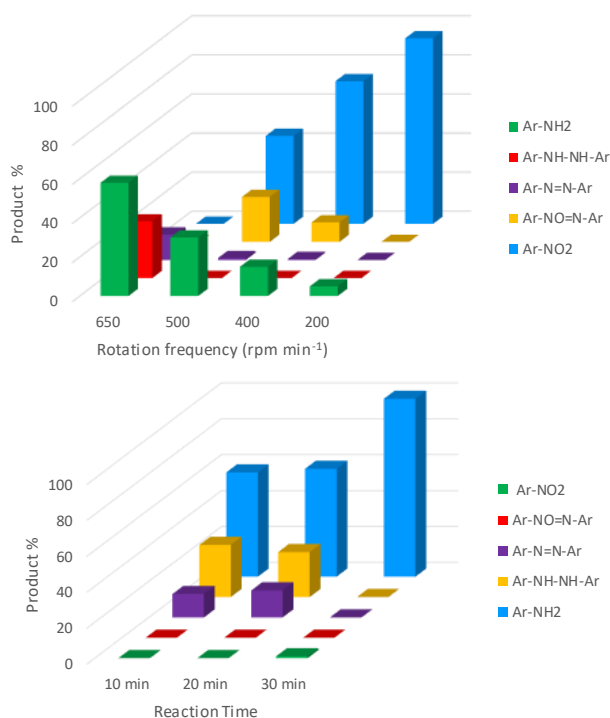


Figure 1. Influence of rotation frequency (top) and milling time (bottom) on conversion to aniline. Reaction conditions: nitrobenzene (0.5 mmol), hydrate hydrazine (30 eq) KOH (1 mmol), alumina (1 g), stainless steel jar, 1500 balls ($\phi = 2$ mm) and 48 balls ($\phi = 5$ mm); rpm and reaction time were varied as described in the graphs.

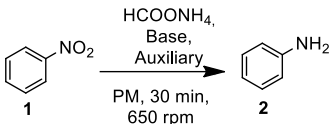
Table 2. Influence of ball size and number on reaction yield^a

Entry	Ball Number		Active surface Area ^c (mm ²)	Yield (%) ^b
	Small ($\phi = 2$ mm)	Medium ($\phi = 5$ mm)		
1	1500	48	22608	>99
2	1500	-	18440	65
3	-	48	3768	3
4	2250	-	27660	33
5	-	144	11304	95

^a Reaction conditions: nitrobenzene (0.5 mmol), hydrate hydrazine (30 eq) KOH (1 mmol), alumina (1 g), stainless steel jar, 650 rpm, 30 min; ^b Isolated yield. ^c Active surface area = surfaceballs

Ammonium formate, a safer and less toxic hydrogen source, was tested in order to improve the protocol's sustainability.⁴⁷ As shown in Table 3, the influence of alumina and the base on reaction yield was tested in the PM at 650 rpm for 30 min for optimisation purposes. A 97% yield was reached (Table 3, Entry 3) when the reaction was performed in the presence of the grinding agent and KOH base. The optimised procedure was then repeated with a selection of nitrobenzene derivatives to broaden the scope of the study. The reaction protocol was performed in the presence of nitrobenzene derivatives (0.5 mmol), KOH (1 mmol), HCOONH₄ (8 eq), alumina (1 g), in the planetary ball mill at 650 rpm for 30 min.

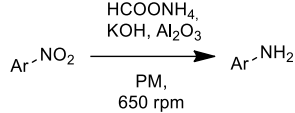
Table 3. Reduction of nitrobenzene with ammonium formate under various conditions



Entry ^a	Base	Al ₂ O ₃	Ar-NH ₂ (%) ^b	Ar-NO ₂ (%) ^b
1	-	-	0	100
2	-	1 g	23	77
3	KOH (8eq)	1 g	97	0

^a Reaction conditions: nitrobenzene (0.5 mmol), ammonium formate (30 eq) 30 min, 650 rpm, stainless steel jar, 1500 balls ($\phi = 2$ mm) and 48 balls ($\phi = 5$ mm). ^b Determined by GC-MS.

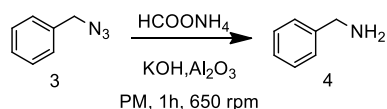
High selectivities and yields were achieved with a number of both electron poor and electron rich substrates (See Table 4).

Table 4. Screening of the mechanochemical reduction of various nitrobenzene derivatives with ammonium formate^a.


Entry	Nitrobenzene	Time (h)	Yield ^b % (Conv) ^c	Entry	Nitrobenzene	Time (h)	Yield ^b % (Conv) ^c	Entry	Nitrobenzene	Time (h)	Yield ^b % (Conv) ^c
1		0.5	97 (100)	5 ^d		1.5	98 (100)	9		1	97 (100)
2		1	98 (100)	6 ^e		2	30 (30)	10		1.5	91 (100)
3		1	92 (100)	7 ^e		2	50 (100)	11		1	95 (100)
4		1.5	93 (100)	8		2	95 (100)				

^a Reaction conditions: nitrobenzene derivatives (0.5 mmol), ammonium formate (30 eq), KOH (1 mmol), basic Al₂O₃ (1 g), 650 rpm, 30 min, stainless steel jar (50 mL), 1500 balls ($\phi = 2$ mm) and 48 balls ($\phi = 5$ mm); ^b Isolated yield, compound purity proved by ¹H-NMR and ¹³C-NMR (see Supporting Info); ^c Determined by GC-MS; ^d The reaction was carried out with 16 mmol KOH; ^e The reaction was carried out with 160 mmol ammonium formate and 16 mmol KOH, milling was maintained for 1h

The reduction of azido derivatives was also attempted in order to broaden the scope of the study. The reduction of benzylazide with ammonium formate was selected as the model reaction (Scheme 1).

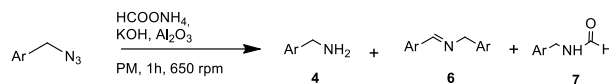


Scheme 1. Synthetic scheme for the reduction of benzyl azide with ammonium formate.

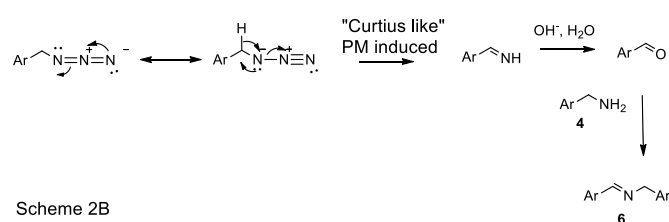
This approach to benzylamine synthesis involves secondary competitive reactions, as the thermal decomposition of organic azides to imines gives benzaldehyde,⁴⁹ and the consequent formation of *N*-benzylidenebenzylamine **6**^{50,51}. In fact it is known that Curtius-like rearrangement of benzylazido afforded to the imine that we presumed to be precursor of benzaldehydes and

Shiff base **6** as well (see Scheme 2A and 2B). In the presence of ammonium formate the formylation of the benzylamine with formic acid salts is a secondary reaction and was observed ⁵² (product **7**). Ammonium formate and sodium formate were tested in order to further our knowledge of how reaction condition influence product distribution. Both silica and alumina were used as auxiliaries and the reaction was tested in presence and in absence of base. Results can be seen in Table 5. In a preliminary experiment, the stability of benzylazide was studied by subjecting it to milling in the stainless steel jar with alumina. As described in Table 5 (Entry 1), complete benzylazide conversion was observed after 1 hour at 650 rpm and the treatment resulted in the production of a number of side products, including benzaldehyde, benzylidenebenzylamine **6**, benzamide and benzylalcohol, which were identified. As previously discussed by Y. Sawama *et al.*,^{19,53} the components (Fe, Cr, Ni etc.) of the stainless steel balls and the planetary ball mill vessel act as the hydrogenation catalyst as they facilitate the generation of hydrogen from water and/or organic materials. When benzyl azide was milled with ammonium formate, KOH and alumina, it selectively gave *N*-benzylformamide (**7**) in a 70% yield (Table 5, Entry 3). However, without the base, about 50% of the starting material was recovered unconverted (Table 5,

Entry 5). To avoid the formylation of benzylamine, the protic ammonium salt was replaced with the sodium analogue. These conditions led to formamide production being reduced to 4%, while the major product was formed from the condensation of benzaldehyde and benzylamine (product **6**; Table 5, entry 6). The *N*-benzylformamide yield increased, because of the acidity of the grinding powder, when silica was used as the grinding auxiliary with sodium formate (Table 5, Entry 8).



Scheme 2A



Scheme 2B

Scheme 2A. Schematic representation of the reduction of benzyl azide in the PM with ammonium formate and production of side products. Scheme 2B schematic representation of Curtius-like mechanism to obtain product **6** from benzylazide

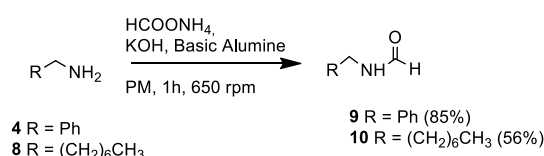
Table 5. Study of benzyl azide reduction with ammonium formate.

Entry	Reducing agent	Reaction conditions	Ar-CH ₂ -N ₃ (%) ^b 3	Ar-CH ₂ -NH ₂ (%) ^b 4	Ar-CHO (%) ^b 5	Ar-CH=N-CH ₂ -Ar (%) ^b 6	Ar-CH ₂ -NH-CHO (%) ^b 7	Ar-CH ₂ -OH (%) ^b
1	-	Al ₂ O ₃ , PM, ^a 1h, 650 rpm	-	3	-	35	-	16
2	-	Al ₂ O ₃ , 80°C, o.n ^c	90	-	9 ^e	-	-	-
3	HCOONH ₄	Al ₂ O ₃ /KOH, PM, ^a 650 rpm, 1h	3	7	5	8	70	-
4	HCOONH ₄	Al ₂ O ₃ /KOH, 80 °C, o.n	37	-	-	-	4	58
5	HCOONH ₄	Al ₂ O ₃ , PM, ^a 650 rpm, 1h	49	14	3	10	27	-
6	HCOONa	Al ₂ O ₃ , ^d PM, ^a 650 rpm, 1h	-	-	6	84	4	2
7	HCOONa	Al ₂ O ₃ , 80°C, o.n	84	-	-	-	-	16
8	HCOONa	SiO ₂ , PM, ^a 650 rpm, 1h-	1	9	4	42	30	-

^a Reaction conditions: benzyl azide (0.5 mmol), ammonium formate (15 mmol when added), sodium formate (10 mmol when added), KOH (1 mmol when added), grinding auxiliary (1 g), 1 h, 650 rpm, stainless steel jar (50 mL), 1500 balls ($\varnothing = 2$ mm) and 48 balls ($\varnothing = 5$ mm); ^b Determined by GC-MS; ^c MeOH was added to facilitate powder mixing; ^d Basic Al₂O₃ was dried in an oven before use; ^e the aldehyde was converted to dimethyl acetal and emiacetal.

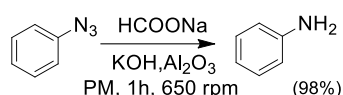
The most selective reactions were performed under conventional conditions for the sake of comparison; benzylazide **3** (1 mmol), and either ammonium formate (30 mmol) or sodium formate (20 mmol), and MeOH (1 mL) were heated at 80°C (Table 4 entries 2,4,7). Methanol was necessary to ensure the efficient mixing of powders. Benzyl azide was found to be quite stable at 80 °C with Al₂O₃ and only 10% was converted to benzaldehyde, in the form of dimethyl acetal and hemiacetal, after one night. Only 4% *N*-formyl benzylamine was observed when the reduction was repeated under conventional conditions in the presence of ammonium formate, while only the benzyl alcohol was produced from the reduction of

benzaldehyde using sodium formate. Mechanochemistry's efficacy in producing *N*-formyl derivatives is proven by the direct formylation of benzyl- and octylamine in the ball mill, as described in Scheme 3. The desired products were obtained in 85% and 56% yields, respectively and interestingly we observed that under mechanochemical activation the formamide derivative resulted stable to hydrolysis of the amido moiety.



Scheme 3. Schematic representation of the formylation of octyl- and benzyl amine with ammonium formate in the PM.

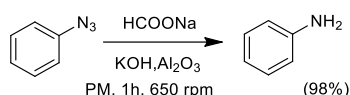
Since the degradation of benzylazide involved the benzylic position, and the formylation side reaction was mainly facilitated by the nucleophilicity of the alkyl amine, we decided to test reduction with sodium formate, starting from aryl azides, which are more stable and less nucleophilic (Scheme 4). The reaction was performed in the presence of KOH because the base accelerates the reaction without affecting the purity of the desired product.



Scheme 4. Synthetic scheme for the reduction of an aryl azide using sodium formate. Reaction conditions: Phenyl azide (0.5 mmol), sodium formate (10 mmol), KOH (1 mmol), grinding auxiliary (1 g), 1 h, 650 rpm; stainless steel jar (50 mL), 1500 balls ($\phi = 2$ mm) and 48 balls ($\phi = 5$ mm)

Gratifyingly, the reaction afforded the desired aniline in a 98% yield and its versatility was evaluated over a small series of differently substituted aryl azides. The azides were prepared according to a previously reported procedure,⁵⁴ using CuSO_4 as the catalyst for the cross coupling of aryl boronic acid with sodium azide under mild reaction conditions. As described in Table 6, high yields were achieved in all cases, chlorobenzene was not affected by the dehalogenation reaction and ortho substituted derivatives were demonstrated to be reactive.

Table 6 Screening of the mechanochemical reduction of aryl azide derivatives with sodium formate^a



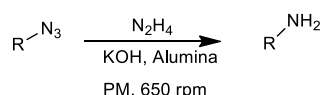
Entry	Aryl azides	Time (h)	Yield ^b % (Conv) ^c
1		1.5	98 (100)
2		1.5	85 (98)
3		1	100 (100)
4		1	87 (92)
5		1.5	95 (98)

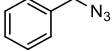
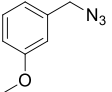

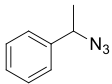
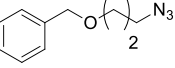

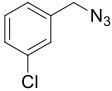

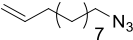
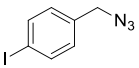
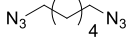
^a Reaction conditions: aryl azide (0.5 mmol), sodium formate (10 mmol), KOH (1 mmol), basic Al_2O_3 (1 g), 650 rpm, stainless steel jar (50 mL), 1500 balls ($\phi = 2$ mm) and 48 balls ($\phi = 5$ mm); ^b Isolated yield, compound purity proven by $^1\text{H-NMR}$ and $^{13}\text{C-NMR}$ (see Supporting Info); ^c Determined by GC-MS.

In order to prove the efficacy of the PM in the reduction of benzyl and alkyl azides, hydrazine was used as the reducing agent instead of formate salts. For organic azides to be manipulable or nonexplosive, the rule is that the number of nitrogen atoms must not exceed that of carbon therefore the experiments were performed with benzyl azides or long chain alkyl derivatives.^{55,56} As described in Table 7, the reaction quantitatively provided the desired set of 11 amines. Table 7 shows that various benzylic and linear azides with different functional groups can be reduced in 1h under the optimised reaction conditions. The -OMe and -Cl groups were unaffected, while *p*-iodobenzyl azide was reduced to benzylamine. Alkyl azides, and not just their benzylic counterparts, were efficiently reduced. In the presence of azido derivatives with a double bond, less than 10% amino alkane was detected.

Finally an ICP analysis was performed to detect the metals released during the reduction. The model reaction of reduction of nitrobenzene with ammonium formate and alumina was performed in 0.5 mmol scale. Cr was detected in 1.32 ± 0.3 g/kg, Fe 9.15 ± 1.6 g/kg and Ni in 9.15 ± 1.6 mg/kg.

Table 7. Screening of the mechanochemical reduction of alkyl benzene derivatives with hydrazine^a



Entry	Alkyl azides	Time (h)	Yield ^b % (Conv) ^c	Entry	Alkyl azides	Time (h)	Yield ^b % (Conv) ^c	Entry	Alkyl azides	Time (h)	Yield ^b % (Conv) ^c
1		1	98 (100)	5		1	99 (100)	9		1	94 (100)
2		1	100 (100)	6		1	80 (100)	10		1	60 (100)
3		1	100 (100)	7		1	96 (98)	11		1	81 (90)
4 ^d		1	- (100)	8		1	90 (100)				

^a Reaction conditions: aryl benzene (0.5 mmol), hydrazine (15 mmol), KOH (10mmol), Alumina (1 g), 650 rpm, stainless steel jar (50 mL), 1500 balls ($\phi = 2$ mm) and 48 balls ($\phi = 5$ mm); ^b Isolated yield, compound purity proven by ¹H-NMR and ¹³C-NMR (see Supporting Info); ^c Determined by GC-MS; ^d Benzylamine was formed as the product.

Experimental

General Information

All chemicals were purchased from Sigma-Aldrich (Milan, Italy) and used without further purification. Reactions were monitored by TLC on Merck 60 F254 (0.25 mm) plates (Milan, Italy), which were visualized via UV inspection and/or via heating after a spraying with 0.5% ninhydrin in ethanol or phosphomolybdic acid. Mechanochemical reactions were carried out in a Planetary Ball Mill (PM100 Retsch GmbH, Haan, Germany) using 50 mL grinding jars and milling balls (both made from stainless steel). NMR spectra (300 MHz and 75 MHz for ¹H and ¹³C, respectively) were recorded on a Bruker 300 Avance instrument (Milan, Italy) at 25 °C. Chemical shifts were calibrated to the residual proton and carbon resonances of the solvent; DMSO-*d*₆ (δ H = 2.54, δ C = 39.5), CDCl₃ (δ H = 7.26, δ C = 77.16), D₂O (δ H = 4.79). Chemical shifts (δ) are given in ppm, and coupling constants (J) in Hz. GC-MS analyses were performed in a GC Agilent 6890 (Agilent Technologies, Santa Clara, CA, USA) that was fitted with a mass detector Agilent Network 5973 and a 30 m capillary column: i.d. of 0.25 mm and film thickness 0.25 μ m. GC conditions were as follows: injection split 1:20, injector temperature 250 °C, detector temperature 280 °C. Gas carrier: helium (1.2 mL/min), temperature program: from 70 °C (2 min) to 300 °C at 5 °C/min. The cations were determined with a Perkin Elmer Optima 7000 (Perkin Elmer, Norwalk, Connecticut, USA) inductively coupled plasma-optical emission spectrometer (ICP-OES).

General Procedure for the nitrobenzene reduction reaction

The milling jar (50 mL; stainless steel) was equipped with 1500 milling balls ($\phi = 2$ mm, stainless steel) and 48 medium balls ($\phi = 5$ mm, stainless steel). Nitrobenzene (0.5 mmol), ammonium

formate (15 mmol), KOH (1 mmol), and basic Al₂O₃ (1 g) were added in the given order. Milling was performed at 650 rpm for 30 min, 1, 1.5 and 2 hours. After the milling jar was cooled to room temperature, the crude products were transferred and the solid washed with CH₂Cl₂ (3 \times 10 mL) and water (3 \times 10 mL). The desired product was extracted in organic phase, washed with H₂O three times and finally dried (Na₂SO₄). When impure, products were purified by flash chromatography on silica gel (hexane–EtOAc). Products were analysed using ¹H NMR and ¹³C NMR spectroscopy, MS and GC-MS chromatography.

General Procedure for the aryl azide reduction reaction

The milling jar (50 mL; stainless steel) was equipped with 1500 milling balls ($\phi = 2$ mm, stainless steel) and 48 medium balls ($\phi = 5$ mm, stainless steel). The aryl azides (0.5 mmol), sodium formate (15 mmol), KOH (1 mmol), and basic Al₂O₃ (1 g) were added in the given order. Milling was accomplished at 650 rpm for 1 and 1.5 hours. After the milling jar was cooled to room temperature, the crude products were transferred and the solid washed with CH₂Cl₂ (3 \times 10 mL) and water (3 \times 10 mL). The desired product was extracted in organic phase, washed with H₂O three times and finally dried (Na₂SO₄). When impure, products were purified by flash chromatography on silica gel (hexane–EtOAc). Products were analysed using ¹H NMR and ¹³C NMR spectroscopy, MS and GC-MS chromatography.

General Procedure for the alkyl azide reduction reaction

The milling jar (50 mL; stainless steel) was equipped with 1500 milling balls ($\phi = 2$ mm, stainless steel) and 48 medium balls ($\phi = 5$ mm, stainless steel). The alkyl azides (0.5 mmol), hydrazine (15 mmol), KOH (1 mmol) and basic Al₂O₃ (1 g) were added in the given order. Milling was accomplished at 650 rpm for 1 hour. After the milling jar was cooled to room temperature, the

crude products were transferred and the solid washed with CH_2Cl_2 (3×10 mL) and water (3×10 mL). The desired product was extracted in organic phase, washed with H_2O three times and finally dried (Na_2SO_4). When impure, products were purified by flash chromatography on silica gel (hexane–EtOAc). Products were analysed using ^1H NMR and ^{13}C NMR spectroscopy, MS and GC-MS chromatography.

Conclusions

Despite its apparent simplicity, the reduction of nitro compounds constitutes a key and venerable transformation, which extends its importance to the chemical industry. Even though numerous papers and patents have reported on the reduction of nitro derivatives with variable success, selective reduction at the nitro group is not easy to make in the presence of other competing functionalities. In conclusion, we have developed a facile new protocol for selective reduction of nitro and azido derivatives that utilises the, mostly unexplored, mechanochemical approach. To best of our knowledge, no report has yet described hydrogenation without catalyst addition being performed in a ball mill. This method benefits from the use of convenient, cost-effective, environmentally friendly formate salts as hydrogen donors. The ball milling reactions have proven themselves to be efficient, versatile and able to give products in short reaction times at high yields, which are also favoured by the easy workup. Challenging functional groups, such as -I, -Br, -Cl, -CO and -COMe, were well tolerated under the described reaction conditions. The advantages of our method include its metal-free nature, its use of eco-friendly and easily available formate salts as the hydrogen source and the ambient reaction conditions.

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