A Mechanochemical-Assisted Oxidation of Amines to Carbonyl Compounds and Nitriles

A Mechanochemical assisted oxidation of amines to carbonyl compounds and nitriles

Silvia Gaspa,[a] Andrea Porcheddu,[b] Antonio Valentoni,[a] Sebastiano Garroni, [c,d] Stefano Enzo[a] and Lidia De Luca*[a]

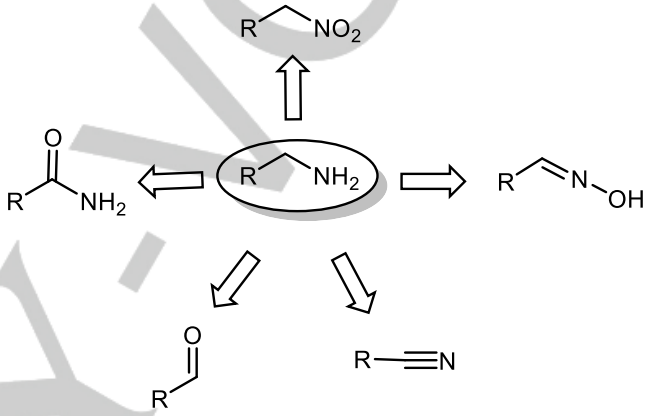
Dedication ((optional))

Abstract: A mild, efficient, metal- and solvent-free oxidation of primary amines to aldehydes, ketones and nitriles under ball-milling conditions is presented. This method has proved to be compatible with various functional groups and requires easily accessible starting materials. Simple filtration of the reaction mixture through a pad of silica gel affords pure aldehydes, ketones and nitriles products.

Introduction

The oxidation of amines is a potent tool to produce a broad range of available synthetic intermediates such as imines, amides, oximes, nitro compounds, nitriles, aldehydes and ketones (Scheme 1).[1]

The conventional route to aldehydes and ketones involves the oxidation of primary and secondary alcohols,[2] but a challenging alternative is the synthesis of carbonyl compounds from readily available and abundant precursors like amines. The existing methodologies, despite their efficiency, suffer from the required use of stoichiometric amounts of toxic metal-containing reagents such as $KMnO_4$,[3] argentic picolinate,[4] $ZnCr_2O_7$ trihydrate,[5] nicotinum dichromate,[6] or the use of palladium-,[7] copper-,[8] ruthenium,[9] metal-based catalysts , and the use of toxic solvents.



Scheme 1. Oxidation of amines

In addition sometimes these methodologies are affected by poor yields, by overoxidation of the carbonyl products to carboxylic acids or by the side-products formation as imines. For the above mentioned reasons new procedures which make use of metal free reagents and which run under neat conditions result to be particular desirable and attractive especially because allow to avoid toxic metal contamination in final products and the use of toxic and volatile organic solvents.

Nitriles are used as versatile intermediates in organic synthesis, while can be readily converted to esters, amides and carboxylic acids. Different methodologies have been developed to synthetize nitriles,[10] and, among of them, the preparation of nitriles from amines appears as the most direct and suitable. However the selective oxidation of primary amines to nitriles presents many difficulties, due to the fact that amines are subject to a variety of oxidative processes that yield an array of products.[11] Recently ruthenium[12] and copper[13] catalysed oxidation of amines to nitriles were reported, despite their large substrate scope suffer from low selectivity, the use of toxic solvents and drastic reaction conditions. Other interesting metal-free procedures were reported, but, even if they have a large substrate scope and are high yielding, make use of large

[a] Dipartimento di Chimica e Farmacia, Università degli Studi di Sassari, via Vienna 2, 07100 Sassari, Italy Fax: (+39)-079-229559; phone: (+39)-079-229494;
E-mail: ldeluca@uniss.it
[b] Dipartimento di Scienze Chimiche e Geologiche, Università degli Studi di Cagliari, Cittadella Universitaria, 09042 Monserrato, Italy
[c] International Research Centre in Critical Raw Materials-ICCRAM, University of Burgos, Plaza Misael Banuelos s/n, 09001 Burgos, Spain;
[d] Advanced Materials, Nuclear Technology and Applied Bio/Nanotechnology. Consolidated Research Unit UIC-154. Castilla y Leon. Spain. University of Burgos. Hospital del Rey s/n, 09001 Burgos, Spain

Supporting information for this article is given via a link at the end of the document.((Please delete this text if not appropriate))

excesses of oxidants and of bases that makes these procedures impractical for large-scale synthesis.[14]

In this context the ball-milling synthesis has draw significant interest in the scientific community due to its advantages over traditional solution-based methods.[15] The major benefit of this technology is that it is solvent-free and it allows to minimize any traditional workup.[16] Higher yields of reaction, higher selectivity of process, less byproducts, and minimum purification requirements are additional benefits of these procedures.[17] For these reasons we have decided to investigate a new approach to oxidize amines under ball-milling conditions.[18]

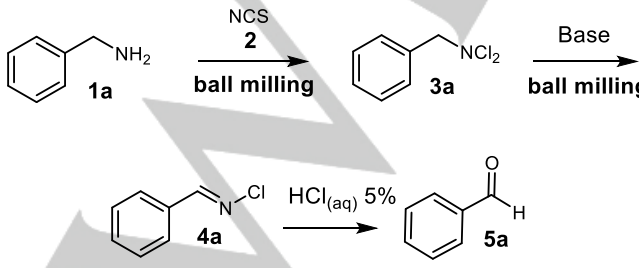
Results and Discussion

Oxidation of primary benzylamine to carbonyl compounds

As part of our on-going efforts to design new synthetic methodologies for the preparation of aldehydes and ketones,[19] we have developed a highly useful procedure for converting primary amines to aldehydes and ketones under ball-milling and solvent-free conditions at room temperature. To the best of our knowledge this is the first example of an oxidative transformation of amines to carbonyl compounds trough a mechanochemical assisted procedure.

We started our investigation by mixing benzylamine (Table 1, **1**, 1.5 mmol) with *N*-chlorosuccinimide[20] (NCS) (Table 1, **2**, 3 mmol) for 10 min at room temperature, sealing the two reagents in a Zirconia jar (50 mL), containing two balls (d = 11.2 mm) of the same material. The corresponding dichloramine **3a** was quantitatively formed. Then triethylamine (4.5 mmol) was added and the mixture was subjected to mechanical treatment for further 10 minutes at room temperature. Upon completion of the ball milling process and after an hydrolysis carried out with $HCl_{(aq)}$ 5%, benzaldehyde **5a** was obtained in 66 % of yield (Table 1, entry 1). In order to find the optimum reaction conditions the quantity of triethylamine was decreased to 3.0 mmol (Table 1, entry 2) and to 2.25 mmol (Table 1, entry 3) and the desired aldehyde **2** was obtained respectively in 70 % and 82 % yield. Different bases were also screened: pyridine (Table 1, entry 4, 3.0 mmol) giving the product **5a** in 40% yield, while $NaOH_{aq}$ (2mL, 1.5 M) (Table 1, entry 5, 3 mmol), K_2CO_3 (Table 1, entry 6, 4.5 mmol), MgO (Table 1, entry 7, 4.5 mmol) did not furnish the benzaldehyde **5a**, but the dichloroamine **3a** was recovered.

Table 1. Screening of Reaction Conditions

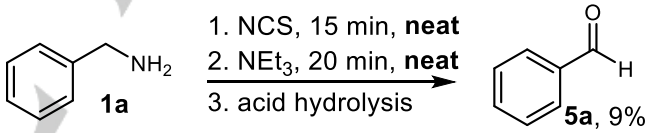


entry	base	mmol(base)	Yield[a]
1	NEt_3	4.5	66
2	NEt_3	3.0	70
3	NEt_3	2.25	82
4	pyridine	3.0	40
5	$NaOH_{aq}$	3.0	-
6	K_2CO_3	4.5	-
7	MgO	4.5	-

[a] Yield refers to isolated product

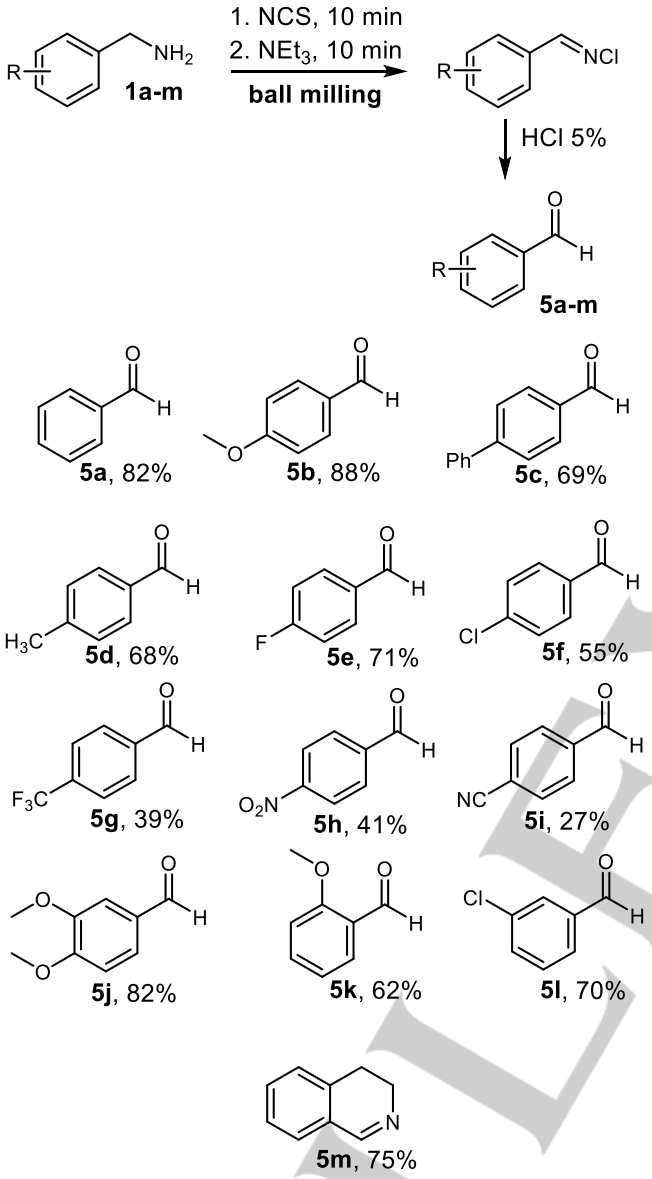
A comparison between neat conditions and ball milling was carried out, showing a better performance of the ball milling assisted process.

The method was performed for benzylamine (Scheme 2, **1a**, 1.5 mmol) in the presence of *N*-chlorosuccinimide (NCS) (Scheme 2, **2**, 3 mmol) under solvent-free (neat) conditions at room temperature for 15 min, then triethylamine (2.25 mmol) was added and the reaction mixture was allowed to stir under solvent-free (neat) conditions at room temperature for 20 min, and after an acid hydrolysis benzaldehyde **5a** was obtained in 9 % of yield.



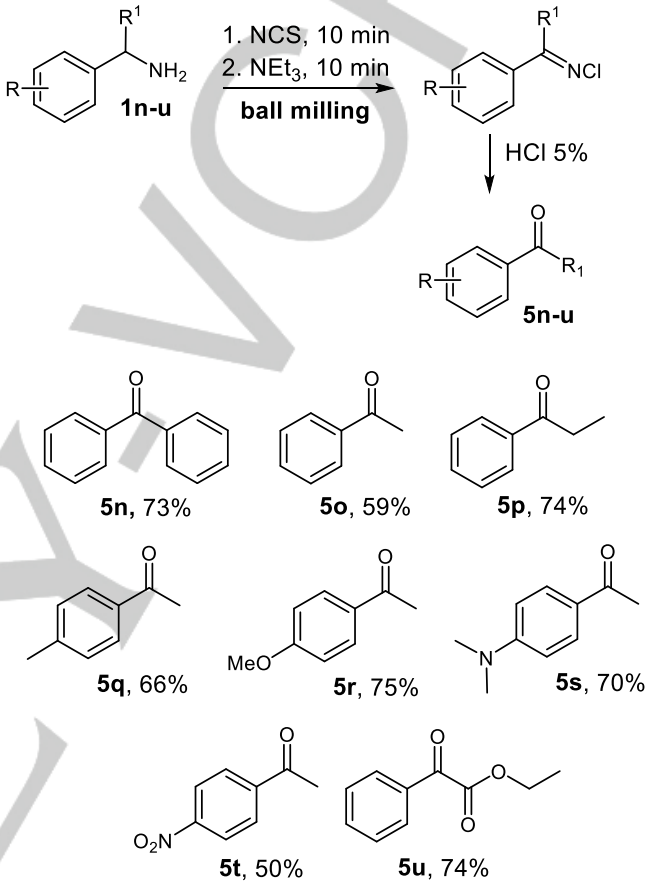
Scheme 2. Oxidation of benzylamine to benzaldehyde under neat conditions.

After the reaction conditions were optimised (Table 1, entry 3), the amine scope of the reaction was tested (Scheme 3). In general, all reactions proceeded without any significant side products, no overoxidation of aldehydes to carboxylic acids was observed and the corresponding carbonyl compounds **5a-m** were obtained in satisfactory yields.



Scheme 3. Oxidation of amines to aldehydes: amines scope

Reactions of benzyl amines having electron-donating substituents on the aromatic ring (Scheme 3, products **5b**, **5c**, **5d**, **5j** and **5k**) give better results to those of amines having electron with-drawing substituents (Scheme 3, products **5e**, **5f**, **5g**, **5h** and **5i**).
Benzylamines bearing substituent in the ortho-position are also suitable substrates for this process (Scheme 3, product **5k**).
The reaction carried out on benzylamine with halide substituents on the aromatic ring (Scheme 3, products **5e**, **5f** and **5l**) gave the corresponding aldehydes, which could be further transformed by traditional cross-coupling reactions. The oxidation of 1,2,3,4-tetrahydroisoquinoline, a cyclic amine, notably gave selectively only 3,4-dihydroisoquinoline, the corresponding conjugated cyclic imine (Scheme 3, product **5m**). The present procedure was applied to aliphatic amines, but at the end of the entire procedure the corresponding *N*-dichloroamines were recovered and the corresponding aldehydes were not obtained.



Scheme 4. Oxidation of amines to ketones: amines scope

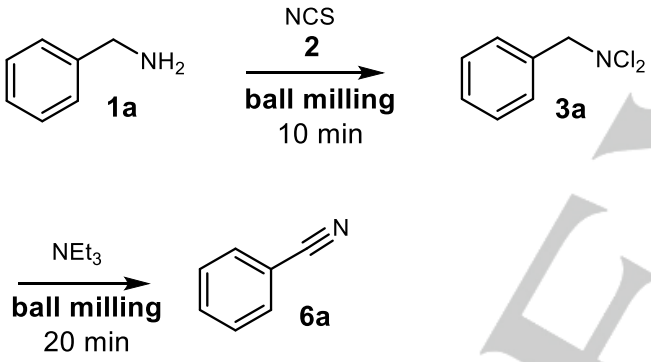
α-Substituted benzylamines were successfully transformed into corresponding ketones *via* this oxidative procedure. Both symmetrical and unsymmetrical α-substituted benzylamines were easily oxidized to corresponding ketones (Scheme 4, products **5n**, **5o**, **5p**, **5q, 5r, 5s, 5t** and **5u**). α-Substituted benzylamines having both electron-donating substituents and electron with-drawing on the aromatic ring work well in this procedure. Finally, the gram scale synthesis of the product **5a** was performed. Under optimized conditions 1.0 g of benzylamine **1a** (7.1 mmol) was mixed with *N*-chlorosuccinimide (NCS) (1.89 g, 14.1 mmol) and then milled for 10 min in a Zirconia jar (50 mL). The corresponding dichloramine **3a** was quantitatively formed. Then triethylamine (1.48 mL,10.6 mmol) was added and the mixture was subjected to mechanical treatment for further 10 minutes at room temperature. Upon completion of the ball milling process and after an hydrolysis carried out with $HCl_{(aq)}$ 5%, benzaldehyde **5a** was obtained in 83 % of yield. Yield and purity remained analogous to the small-

scale reaction, providing the flexibility and scalability of the methodology.

The oxidation of primary benzylic amines to nitriles

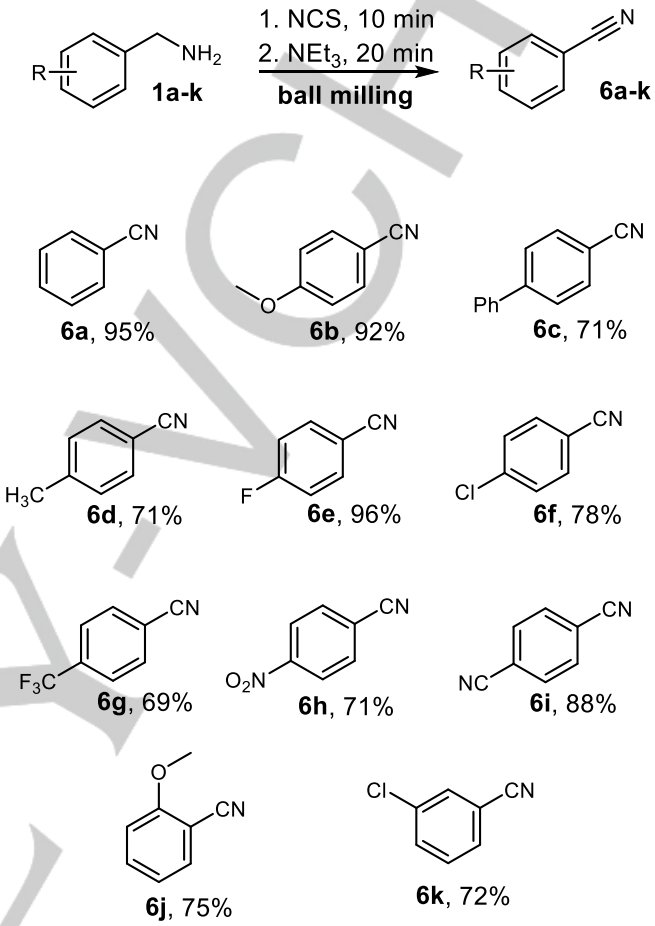
After the successful oxidation of primary benzylic amines to aldehydes and ketones, we have investigated the possibility to transform amines into nitriles under ball-milling and solvent-free conditions at room temperature. The same methodology used to oxidize the amines to carbonyl compounds may be employed to allow a one-pot oxidation of amines to nitriles by means of an increase in the time of ball milling and of triethylamine amount.

We started our investigation by treating benzylamine (Scheme 5, **1a**, 1.5 mmol) with *N*-chlorosuccinimide (NCS) (Scheme 5, **2**, 3 mmol) and the reaction was carried out in a shaker mill equipped with a ZrO_2-milling jar (50 ml), containing two balls (d = 11.2 mm) of the same material which was ball-milled for 10 min at room temperature. The corresponding dichloramine **3** was quantitatively formed. Then a triethylamine (4.5 mmol) was added and the mixture was subjected to mill for 20 minutes at room temperature. Upon completion of the ball milling process benzonitrile **6a** was obtained in 95% of yield (Scheme 5, product **6a**).



Scheme 5. Oxidation of amines to nitriles

Then the scope of the methodology was tested. Generally all reactions proceeded without any significant side products, and the corresponding nitriles **6a-k** were obtained in satisfactory yields.

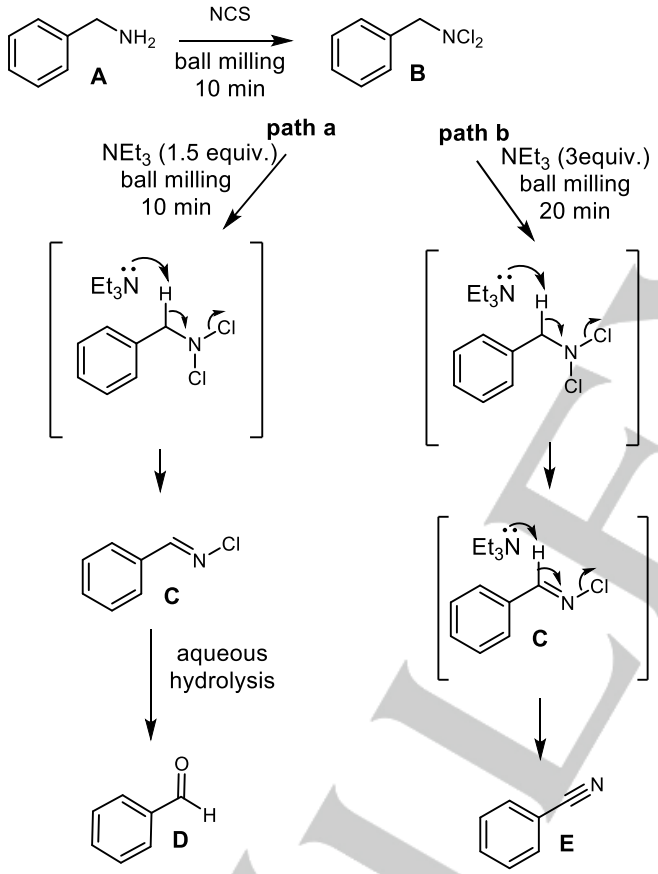


Scheme 6. Oxidation of amines to nitriles: amines scope

Reactions of benzyl amines having electron-donating substituents on the aromatic ring (Scheme 6, products **6b**, **6c** and **6d**) give comparable yields to those of amines having electron with-drawing substituents (Scheme 6, products **6e**, **6f**, **6g**, **6h**, **6i** and **6k**). Benzylamines bearing substituent in the ortho-position are also suitable substrates for this process (Scheme 6, product **6j**). The reaction carried out on benzylamine with halide substituents on the aromatic ring (Scheme 6, products **6e**, **6f** and **6k**) gave the corresponding benzonitriles, which could be further transformed by traditional cross-coupling reactions. The gram scale synthesis of the product **6a** was investigated. Under optimized conditions for the preparation of nitriles 1.0 g of benzylamine **1a** (7.1 mmol) was mixed with *N*-chlorosuccinimide (NCS) (1.89 g, 14.1 mmol) and then milled for 10 min in a Zirconia jar (50 mL). Then triethylamine (2.95 mL, 21.2 mmol) was added and the mixture

was subjected to mechanical treatment for further 20 minutes at room temperature. Upon completion of the ball milling process benzonitrile **6a** was obtained in 94% of yield. Also in this case the yield and purity remained analogous to the small-scale reaction.

A plausible reaction sequence is shown in Scheme 7. Benzylamine **A**, reacted with *N*-chlorosuccinimide (NCS) by ball milling (10 min), is transformed to *N*-dichlorobenzylamine **B** which was isolated and characterized, probably *via* a radical pathway. When *N*-dichlorobenzylamine **B** is reacted with 1.5 equiv. of NEt_3 by ball milling (10 min) (Scheme 7, **path a**), is transformed[21] to *N*-chlorobenzylimine **C** which was isolated and characterized.[22] After aqueous hydrolysis *N*-chlorobenzylimine **C** is converted to corresponding benzaldehyde **D**. Instead when *N*-dichlorobenzylamine **B** is reacted whit 3 equiv. of NEt_3 by ball milling (20 min) (Scheme 7, **path b**), is transformed to benzonitrile **E**.



Scheme 7. Proposed reaction sequence of carbonyl compounds and nitriles formation.

Conclusions

In summary, we have developed a mild, efficient and metal-free method for the synthesis of aldehydes, ketones and nitriles from primary amines under ball-milling conditions, which may constitute a significant addition in mechanochemical synthesis. This method has proved to be compatible with various functional groups and requires easily accessible starting materials.

Experimental Section

General Information

All reagents and solvents were as obtained by commercial source. All solvents were dried by usual methods and distilled under Argon. Short chromatography was generally performed on silica gel (pore size 60 Å, 32-63 nm particle size) with 4 cm column's diameter with 5 cm of silica gel, and reactions were monitored by thin-layer chromatography (TLC) analysis was performed with Merck Kieselgel 60 F254 plates and visualized using UV light at 254 nm, $KMnO_4$ and 2,4-DNP staining. An 8000M Mixer/Mill®, ball-milling apparatus was used for all reactions with a rotation frequency of 875 rpm. ^1H NMR and ^{13}C NMR spectra were measured on a Bruker Avance III 400 spectrometer (400 MHz or 100 MHz, respectively) using $CDCl_3$ solutions and TMS as an internal standard. Chemical shifts are reported in parts per million (ppm, d) relative to internal tetramethylsilane standard (TMS, d 0.00). The peak patterns are indicated as follows: s, singlet; d, doublet; t, triplet; m, multiplet; q, quartet; dd, doublet of doublets; br, broad. The coupling constants, *J*, are reported in Hertz (Hz). Melting points were determined in open capillary tubes and are uncorrected.

General Procedure to oxidation of primary benzylamine to carbonyl compounds:

Benzylamine (0.212 g, 1.5 mmol) and *N*-chlorosuccinimide (0.400 g, 3 mmol) were milled in a Zirconia vial (50 mL), containing two balls (d = 11.2 mm) of the same material. The reagents were then ball milled in a shaker milling device for 10 min at room temperature (monitored by TLC the disappearance of benzylamine). Then, NEt_3 (0.227 g, 2.25 mmol) was added and the mixture was subjected to mill further for 10 minutes at room temperature. Upon completion of the ball milling process, the jar was opened and to the reaction mixture was added 10 mL of THF and transferred in a round bottom flask for the hydrolysis. To the mixture was added 15 mL of $HCl_{(aq)}$ 5% and subjected to stir for 2 hours at room temperature and then, extracted there times with 10 mL of CH_2Cl_2. The combined organic phase were dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude product was purified through a short chromatography column (hexane/ ethyl acetate).

Compound characterizations 5a-5u:

Benzaldehyde (5a):[23] Colorless oil; (0.130 g, 82 % yield). The desired pure product was obtained after short column chromatography (R_f = 0.314 hexane/ethyl acetate 4.5/0.5). ^1H NMR (400 MHz, $CDCl_3$) δ: 10.00 (s, 1H), 7.86 (d, *J* = 7.5 Hz, 2H), 7.61 (t, *J* = 7.1 Hz, 1H), 7.52 (d, *J* = 7.7 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 192.2, 136.3, 134.3, 129.6, 128.9.

4-methoxybenzaldehyde (5b):[23] Colorless oil; (0.180 g, 88 % yield). The desired pure product was obtained after short column chromatography (R_f = 0.344 hexane/ethyl acetate 4/1). ^1H NMR (400 MHz, $CDCl_3$) δ: 9.83 (s, 1H), 7.78 (d, *J* = 8.5 Hz, 2H), 6.95 (d, *J* = 8.6 Hz, 2H), 3.83 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 190.6, 164.4, 131.8, 129.8, 114.1, 55.4.

[1,1'-biphenyl]-4-carbaldehyde (5c):[24] White solid; (0.189 g, 69 % yield); m.p. 56 - 58 °C. The desired pure product was obtained after short column

chromatography (R_f = 0.4 hexane/ethyl acetate 4.5/0.5). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.07 (s, 1H), 7.96 (d, *J* = 8.1 Hz, 2H), 7.76 (d, *J* = 8.0 Hz, 2H), 7.64 (d, *J* = 7.6 Hz, 2H), 7.49 (t, *J* = 7.5 Hz, 2H), 7.42 (t, *J* = 7.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 191.9, 147.2, 139.7, 135.2, 130.2, 129.0, 128.5, 127.7, 127.3.

4-methylbenzaldehyde (5d):[25] Colorless oil; (0.122 g, 68 % yield). The desired pure product was obtained after short column chromatography (R_f = 0.613 hexane/ethyl acetate 4.5/0.5). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.96 (s, 1H), 7.77 (d, *J* = 8.0 Hz, 2H), 7.33 (d, *J* = 7.8 Hz, 2H), 2.44 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 192.0, 145.5, 134.2, 129.8, 129.7, 21.9.

4-fluorobenzaldehyde (5e):[26] Colorless oil; (0.132 g, 71 % yield). The desired pure product was obtained after short column chromatography (R_f = 0.59 hexane/ethyl acetate 4.5/0.5). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.91 (s, 1H), 7.85 (dd, *J* = 8.6, 5.6 Hz, 2H), 7.15 (t, *J* = 8.5 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 190.3, 166.3 (d, *J* = 255 Hz), 132.8 (d, *J* = 2.4 Hz), 132.5 (d, *J* = 9.6 Hz), 116.2 (d, *J* = 22.2 Hz).

4-chlorobenzaldehyde (5f):[27] White solid; (0.116 g, 55 % yield); m.p. 46 - 47.5 °C. The desired pure product was obtained after short column chromatography (R_f = 0.451 hexane/ethyl acetate 4.5/0.5). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.97 (s, 1H), 7.81 (d, *J* = 8.4 Hz, 2H), 7.50 (d, *J* = 8.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 190.8, 140.9, 134.7, 130.8, 129.4.

4-(trifluoromethyl)benzaldehyde (5g): Colorless oil; (0.102 g, 39 % yield). The desired pure product was obtained after short column chromatography (R_f = 0.433 hexane/ethyl acetate 4.5/0.5). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.10 (s, 1H), 8.01 (d, *J* = 8.0 Hz, 2H), 7.81 (d, *J* = 8.0 Hz, 2H).[28] ^{13}C NMR (100 MHz, $CDCl_3$) δ: 191.1 , 138.7, 135.6 (q, *J* = 37.5 Hz), 129.9, 126.1 (q, *J* = 7.5 Hz), 123.5 (q, *J* = 270 Hz).[29]

4-nitrobenzaldehyde (5h):[25] Yellow solid; (0.093 g, 41 % yield); m.p. 106 - 107 °C. The desired pure product was obtained after short column chromatography (R_f = 0.385 hexane/ethyl acetate 4.5/0.5). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.16 (s, 1H), 8.39 (d, *J* = 8.6 Hz, 2H), 8.07 (d, *J* = 8.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.2, 151.1, 140.0, 130.5, 124.3.

4-formylbenzonitrile (5i):[30] White solid; (0.053 g, 27 % yield); m.p. 102 - 103 °C. The desired pure product was obtained after short column chromatography (R_f = 0.333 hexane/ethyl acetate 4/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.07 (s, 1H), 7.97 (d, *J* = 8.1 Hz, 2H), 7.82 (d, *J* = 8.1 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 190.6, 138.6, 132.8, 129.7, 117.6, 117.4.

3,4-dimethoxybenzaldehyde (5j):[31] White solid; (0.204 g, 82 % yield); m.p. 42 - 43 °C. The desired pure product was obtained after short column chromatography (R_f = 0.379 hexane/ethyl acetate 3.5/1.5). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.84 (s, 1H), 7.45 (dd, *J* = 8.2, 1.9 Hz, 1H), 7.40 (d, *J* = 1.8 Hz, 1H), 6.97 (d, *J* = 8.2 Hz, 1H), 3.96 (s, 3H), 3.93 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 190.8, 154.4, 149.6, 130.1, 126.8, 110.4, 108.9, 56.1, 56.0.

2-methoxybenzaldehyde (5k):[27] Yellow oil; (0.126 g, 62 % yield). The desired pure product was obtained after short column chromatography (R_f = 0.333 hexane/ethyl acetate 4.8/0.2). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.47 (s, 1H), 7.82 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.56 – 7.52 (m, 1H), 7.03 – 6.97 (m, 2H), 3.92 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 189.7, 161.8, 135.9, 128.5, 124.8, 120.6, 111.6, 55.6.

3-chlorobenzaldehyde (5l):[32] Colorless oil; (0.148 g, 70 % yield). The desired pure product was obtained after short column chromatography (R_f = 0.548 hexane/ethyl acetate 4.5/0.5). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.88 (s, 1H), 7.75 – 7.70 (m, 1H), 7.67 (d, *J* = 7.7 Hz, 1H), 7.51 – 7.46 (m, 1H), 7.39 (t, *J* = 7.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 190.5, 137.6, 135.1, 134.0, 130.1, 128.8, 127.7.

3,4-dihydroisoquinoline (5m):[33] Colorless oil; (0.147 g, 75 % yield). The desired pure product was obtained after short column chromatography (R_f = 0.125 hexane/ethyl acetate 1/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.35 (s, 1H), 7.37 (t, *J* = 6.8 Hz, 1H), 7.33 – 7.27 (m, 2H), 7.17 (d, *J* = 7.3 Hz, 1H), 3.79 (t, *J* = 7.2 Hz, 2H), 2.76 (t, *J* = 7.8 Hz ,2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.3, 136.2, 131.0, 128.4, 127.3, 127.2, 127.0, 47.2, 24.9.

Benzophenone (5n):[34] White solid; (0.199 g, 73 % yield); m.p. 47 - 49 °C. The desired pure product was obtained after short column chromatography (R_f = 0.285 hexane/ethyl acetate 4.5/0.5). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.81 (d, *J* = 7.5 Hz, 4H), 7.59 (t, *J* = 7.4 Hz, 2H), 7.48 (t, *J* = 7.5 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 196.7, 137.6, 132.4, 130.0, 128.2.

Acetophenone (5o):[35] Colorless oil; (0.106 g, 59 % yield). The desired pure product was obtained after short column chromatography (R_f = 0.333 hexane/ethyl acetate 4.7/0.3). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.93 (d, *J* = 7.3 Hz, 2H), 7.56 – 7.50 (m, 1H), 7.43 (t, *J* = 7.6 Hz, 2H), 2.57 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 197.9, 137.0, 132.9, 128.4, 128.2, 26.4.

Propiophenone (5p):[36] Colorless oil; (0.149 g, 74 % yield). The desired pure product was obtained after short column chromatography (R_f = 0.354 hexane/ethyl acetate 4.7/0.3). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.95 (d, *J* = 7.8 Hz, 2H), 7.53 (t, *J* = 7.4 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 2H), 2.98 (q, *J* = 7.2 Hz, 2H), 1.21 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 199.8, 135.9, 131.8, 127.5, 126.9, 30.7, 7.2.

1-(p-tolyl)ethan-1-one (5q):[37] Colorless oil: (0.133 g, 66 % yield). The desired pure product was obtained after short column chromatography (R_f = 0.286 hexane/ethyl acetate 4.5/0.5). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.87 (d, *J* = 8.1 Hz, 2H), 7.27 (d, *J* = 8.0 Hz, 2H), 2.59 (s, 3H), 2.42 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 197.8, 143.8, 134.6, 129.2, 128.4, 26.4, 21.5.

1-(4-methoxyphenyl)ethan-1-one (5r): [35] Colorless oil: (0.169 g, 75 % yield). The desired pure product was obtained after short column chromatography (R_f = 0.345 hexane/ethyl acetate 4/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.92 (d, *J* = 8.7 Hz, 2H), 6.92 (d, *J* = 8.8 Hz, 2H), 3.85 (s, 3H), 2.54 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 196.6, 163.4, 130.5, 130.3, 113.6, 55.4, 26.3.

1-(4-(dimethylamino)phenyl)ethan-1-one (5s): [38] White solid: (0.171 g, 70 % yield). m.p. 103 - 104 °C. The desired pure product was obtained after short column chromatography (R_f = 0.345 hexane/ethyl acetate 4/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.87 (d, *J* = 8.9 Hz, 2H), 6.65 (d, *J* = 8.9 Hz, 2H), 3.05 (s, 6H), 2.50 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 196.3, 153.3, 130.5, 125.4, 110.6, 40.0, 25.9.

1-(4-nitrophenyl)ethan-1-one (5~~r~~t):[~~38~~ 39] White solid; (0.124 g, 50 % yield); m.p. 76 - 77 °C. The desired pure product was obtained after short column chromatography (R_f = 0.7 hexane/ethyl acetate 4/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.31 (d, *J* = 8.3 Hz, 2H), 8.11 (d, *J* = 8.7 Hz, 2H), 2.68 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 196.2, 150.4, 141.4, 129.3, 123.8, 27.0.

Ethyl 2-oxo-2-phenylacetate (5~~s~~u):[~~39~~ 40] Yellow oil; (0.198 g, 74 % yield). The desired pure product was obtained after short column chromatography (R_f = 0.3 hexane/ethyl acetate 4.2/0.8). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.00 (d, *J* = 7.6 Hz, 2H), 7.65 (t, *J* = 7.4 Hz, 1H), 7.50 (t, *J* = 7.7 Hz, 2H), 4.45 (q, *J* = 7.1 Hz, 2H), 1.42 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 186.4, 163.8, 134.8, 132.4, 130.0, 128.8, 62.3, 14.1.

General Procedure to oxidation of primary benzylic amines to nitriles 6a-6k:

Benzylamine (0.212 g, 1.5 mmol) and *N*-chlorosuccinimide (0.400 g, 3 mmol) were milled in a Zirconia vial (50 mL), containing two balls (d = 11.2 mm) of the same material. The reagents were then ball milled in a shaker milling device for 10 min at room temperature (monitored by TLC the disappearance of benzylamine). Then, NEt_3 (0.455 g, 4.5 mmol) was added and the mixture was subjected to mill further for 20 minutes at room temperature. Upon completion of the ball milling process, the crude product was purified through ~~a pad of silica gel~~ a short chromatography column (hexane/ ethyl acetate) providing benzonitrile **6a** (0.147g, 95%).

Compound characterizations 6a-6k:

Benzonitrile (6a):[40 41] Colorless oil; (0.147 g, 95 % yield). The desired pure product was obtained after short column chromatography (R_f = 0.314 hexane/ethyl acetate 4.5/0.5). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.66 (d, *J* = 7.5 Hz, 2H), 7.61 (t, *J* = 7.6 Hz, 1H), 7.47 (t, *J* = 7.7 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 132.7, 132.1, 129.1, 118.8, 112.4.

4-methoxybenzonitrile (6b):[40 41] Colorless oil; (0.184 g, 92 % yield). The desired pure product was obtained after short column chromatography (R_f = 0.406 hexane/ethyl acetate 4.3/0.7). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.58 (d, *J* = 7.2 Hz, 2H), 6.94 (d, *J* = 8.4 Hz, 2H), 3.85 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.8, 133.9, 119.2, 114.7, 103.9, 55.5.

[1,1'-biphenyl]-4-carbonitrile (6c):[40 41] Yellow solid; (0.191 g, 71 % yield); m.p. 88 - 89 °C. The desired pure product was obtained after short column chromatography (R_f = 0.4 hexane/ethyl acetate 4.5/0.5). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.74 - 7.67 (m, 4H), 7.59 (d, *J* = 7.4 Hz, 2H), 7.51 - 7.41 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 145.6, 139.1, 132.5, 129.1, 128.6, 127.7, 127.2, 118.9, 110.8.

4-methylbenzonitrile (6d):[41 42] Colorless oil; (0.124 g, 71 % yield). The desired pure product was obtained after short column chromatography (R_f = 0.385 hexane/ethyl acetate 4.5/0.5). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.50 (d, *J* = 8.0 Hz, 2H), 7.23 (d, *J* = 7.5 Hz, 2H), 2.38 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.6, 132.0, 129.8, 119.1, 109.3, 21.8.

4-fluorobenzonitrile (6e):[42 43] Colorless oil; (0.174 g, 96 % yield). The desired pure product was obtained after short column chromatography (R_f = 0.59 hexane/ethyl acetate 4.5/0.5). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.65 (dd, *J* = 8.7, 5.2 Hz, 2H), 7.15 (t, *J* = 8.5 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.9 (d, *J* = 254 Hz), 134.5 (d, *J* = 9 Hz), 117.85, 116.7 (d, *J* = 13 Hz) 108.42 (d, *J* = 22 Hz).

4-chlorobenzonitrile (6f):[40 41] White solid; (0.161 g, 78 % yield); m.p. 91 - 93 °C. The desired pure product was obtained after short column chromatography (R_f = 0.344 hexane/ethyl acetate 4.8/0.2). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.60 (d, *J* = 8.5 Hz, 2H), 7.47 (d, *J* = 8.5 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 139.5, 133.3, 129.7, 117.9, 110.8.

4-(trifluoromethyl)benzonitrile (6g):[41 42] Colorless oil; (0.177 g, 69 % yield). The desired pure product was obtained after short column chromatography (R_f = 0.613 hexane/ethyl acetate 4.5/0.5). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.3 Hz, 2H), 7.76 (d, *J* = 8.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 134.6 (q, *J* = 33.6 Hz), 132.7, 126.2 (q, *J* = 3.7 Hz), 123.1 (q, *J* = 273.5 Hz), 117.4, 116.1.

4-nitrobenzonitrile (6h):[43 44] White solid; (0.157 g, 71 % yield); m.p. 88 - 89 °C. The desired pure product was obtained after short column chromatography (R_f = 0.385 hexane/ethyl acetate 4.5/0.5). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.36 (d, *J* = 8.7 Hz, 2H), 7.89 (d, *J* = 8.7 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.0, 133.4, 124.3, 118.4, 116.8.

Terephthalonitrile (6i):[43 44] White solid; (0.169 g, 88 % yield); m.p. 222 - 223 °C. The desired pure product was obtained after short column chromatography (R_f = 0.333 hexane/ethyl acetate 4/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.79 (s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 132.8, 117.0, 116.7.

2-methoxybenzonitrile (6j):[41 42] Colorless oil; (0.150 g, 75 % yield). The desired pure product was obtained after short column chromatography (R_f = 0.333 hexane/ethyl acetate 4.8/0.2) ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.56 – 7.46 (m, 2H), 7.00 – 6.92 (m, 2H), 3.88 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.0, 134.3, 133.5, 120.6, 116.3, 111.2, 101.4, 55.8.

3-chlorobenzonitrile (6k):[42 43] Colorless oil; (0.148 g, 72 % yield). The desired pure product was obtained after short column chromatography (R_f = 0.548 hexane/ethyl acetate 4.5/0.5). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.67 – 7.63 (m, 1H), 7.61 – 7.54 (m, 2H), 7.43 (t, *J* = 7.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 135.3, 133.2, 131.9, 130.5, 130.3, 117.4, 114.0.

General Procedure to *N,N*-dichloro-1-phenylmethanamine:

Benzylamine (0.212 g, 1.5 mmol) and *N*-chlorosuccinimide (0.400 g, 3 mmol) were milled in a Zirconia vial (50 mL), containing two balls (d = 11.2 mm) of the same material. The reagents were then ball milled in a shaker milling device for 10 min at room temperature (monitored by TLC the disappearance of benzylamine). Upon completion of the ball milling process, the crude product was purified through a short chromatography column (hexane/ ethyl acetate) providing a product.

Compound characterizations:

***N,N*-dichloro-1-phenylmethanamine**:[44 45] White solid; (0.174 g, 66 % yield). The desired pure product was obtained after short column chromatography (R_f = 0.518 hexane/ethyl acetate 4.8/0.2). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.41 (s, 5H), 4.70 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 134.9, 130.0, 129.2, 128.5, 78.9.

General Procedure to (E)-*N*-chloro-1-phenylmethanimine:

Benzylamine (0.212 g, 1.5 mmol) and *N*-chlorosuccinimide (0.400 g, 3 mmol) were milled in a Zirconia vial (50 mL), containing two balls (d = 11.2 mm) of the same material. The reagents were then ball milled in a shaker milling device for 10 min at room temperature (monitored by TLC the disappearance of benzylamine). Then, NEt_3 (0.227 g, 2.25 mmol) was added and the mixture was subjected to mill further for 10 minutes at room temperature.Upon completion of the ball milling process, the crude product was purified through a short chromatography column (hexane/ ethyl acetate) providing a product.

Compound characterizations:

(E)-N-chloro-1-phenylmethanimine:[45 46] White solid; (0.113 g, 54 % yield). The desired pure product was obtained after short column chromatography (R_f = 0.392 hexane/ethyl acetate 4.5/0.5). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.81 (s, 1H), 7.68 (d, *J* = 7.5 Hz, 2H), 7.52 - 7.42 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 172.6, 133.2, 132.1, 129.0, 128.0.

General Procedure to (E)-*N*-chloro-1-phenylmethanimine from *N,N*-dichloro-1-phenylmethanamine:

N,N-dichloro-1-phenylmethanamine (0.264 g, 1.5 mmol) and NEt_3 (0.227 g, 2.25 mmol) were milled in a Zirconia vial (50 mL), containing two balls (d = 11.2 mm) of the same material. The reagents were then ball milled in a shaker milling device for 10 min at room temperature (monitored by TLC the disappearance of *N,N*-dichloro-1-phenylmethanamine). Upon completion of the ball milling process, the crude product was purified through a short chromatography column (hexane/ ethyl acetate) providing (E)-*N*-chloro-1-phenylmethanimine (0.123 g, 59 %).

General Procedure to carbonyl compounds from (E)-*N*-chloro-1-phenylmethanimine:

(E)-*N*-chloro-1-phenylmethanimine (0.209 g, 1.5 mmol) was dissolved in 10 mL of THF and transferred in a round bottom flask for the hydrolysis. To the mixture was added 15 mL of $HCl_{(aq)}$ 5% and subjected to stir for 2 hours at room temperature and then, extracted there times with 10 mL of CH_2Cl_2. The combined organic phase were dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude product was purified through a short chromatography column (hexane/ ethyl acetate) to provide benzaldehyde **5a** (0.134 g, 84%)

General Procedure to nitriles from *N,N*-dichloro-1-phenylmethanamine:

N,N-dichloro-1-phenylmethanamine (0.264 g, 1.5 mmol) and NEt_3 (0.455 g, 4.5 mmol) were milled in a Zirconia vial (50 mL), containing two balls (d = 11.2 mm) of the same material for 20 min at room temperature (monitored by TLC the disappearance of *N,N*-dichloro-1-phenylmethanamine). Upon completion of the ball milling process, the crude product was purified through a short chromatography column (hexane/ ethyl acetate) providing benzonitrile **6a** (0.148 g, 96%).

Acknowledgements

This work was financially supported by Regione autonoma della Sardegna within the project:"Valorizzazione di biomasse d'interesse regionale attraverso processi chimici a basso impatto ambientale"(CRP 72-Bando "Capitale Umano ad Alta Qualificazione. Annualità 2015_L.R. 7 agosto 2007, n°7"). Acknowledgements Silvia Gaspa gratefully acknowledges Sardinia Regional Government for the financial support of her PhD scholarship (P.O.R. Sardegna F.S.E. Operational Programme of the Autonomous Region of Sardinia, European Social Fund 2007– 2013-Axis IV Human Resources, Objective l.3, Line of Activity l.3.1).

Keywords: ball milling • oxidation • aldehydes • ketones • nitriles • mechanochemistry

[1] a) K. C. Nicolau, C. J. N. Mathison, T.Montagnon, *J. Am.Chem. Soc.* **2004**, *126*, 5192-5201; b) G. Chu, C. Li, *Org. Biomol. Chem.* **2010**, *8*, 4716-4719; c) P. Galletti, F. Funiciello, R. Soldati, D. Giacomini, *Adv. Synth. Catal.* **2015**, *357*, 1840-1848; d) V. V. Patil, E. M. Gayakwad, G. S. Shankarling, *J. Org. Chem.* **2016**, *81*, 781-786; e) V. V. Patil, g. S. Shankarling, *J. Org. Chem.* **2015**, *80*, 7876-7883; (f) X. Wu, C. B. Bheeter, H. Neumann, P. H. Dixneuf, M. Beller, *Chem. Commun.* **2012**, *47*, 12237-12239; g) J. W. Kim, K. Yamaguchi, N. Mizuno, *Angew. Chem.***2008**, *120*, 9389-9391: *Angew. Chem. Int. Ed.* **2008**, *47*, 9249-9251; h) Y. Wang, H. Kaboyashi, K. Yamaguchi, N. Mizuno, *Chem. Commun.* **2012**, *48*, 2642-2644.

[2] a) G. Tojo, M. Fernandez in *Oxidation of Alcohols to Aldehydes and Ketones, 1st edn.* Springer, New York, **2006**.

[3] S. S. Rawalay, H. Shechter, *J. Org. Chem.* **1967**, *32*, 3129-3131.

[4] R. G. R. Bacon, W. J. W. Hanna, *J. Chem. Soc.***1965**, 4962-4968.

[5] S. Sabhani, M. F. Maleki, *Synlett* **2010**, 383-386.

[6] S. Sobhani, S. Aryanejad, M. F. Maleki, *Helv. Chim. Acta* **2012**, *95*, 613-617.

[7] S. Chandrasekhar, G. P. K. Reddy, C. Nagesh, C. R. Reddy, *Tetrahedron Lett.* **2007**, *48*, 1269-1271.

[8] a) J. Srogl, S. Voltrova, *Org. Lett.* **2009**, *11*, 843-845; b) S. -i. Naya, T. Niwa, R. Negishi, H. Kobayashi, H. Tada, *Angew. Chem.* **2014**, *126*, 14114-14117; *Angew. Chem. Int. Ed.* **2014**, *53*, 13894-13897.

[9] N. Iqbal, E. J. Cho, *Adv. Synth. Catal.* **2015**, *357*, 2187-2192.

[10] *Comprehensive Organic Transformations*, (Ed. R. C. Larock) Wiley-VCH, Weinheim, **1999**, pp. 819-939.

[11] a) For a review of the oxidation of amines, see: D. H. Rosenblatt,E. Burrows in Supplement F: *The Chemistry of Amino, Nitroso, and Nitro Compounds and Their Derivatives*, Vol. 1, Part 2 (Ed.: S. Patai), Wiley, Chichester, 1982, pp. 1085–1149; b) C. R. Noller in *Textbook of Organic Chemistry* Vol. 3, W. B. Saunders Company, Philadelphia, PA, 1966, p. 229.

[12] a) K. Yamaguchi, N. Mizuno, *Angew. Chem.* **2003,** *115*, 1518-1521; *Angew. Chem. Int. Ed.* **2003**, *42*, 1480-1483; b) Y. Zhang, K. Xu, X. Chen, T. Hu, Y. Yu, J. Zhang, J. Huang, *Catal. Commun.* **2010**, *11*, 951-954; c) S. Venkatesan, A. S. Kumar, J.-F. Lee, T.-S. Chan, J.-M. Zen, *Chem. Eur. J.* **2012**, *18*, 6147-6151; d) M. T. Schumperli, C. Hammond, I. Hermans, *ACS Catal.* **2012**, *2*, 1108-1117; e) E. C. Corker, J. Ruiz-Martinez, A. Riisager, R. Fehrmann, *Catal. Sci. Technol.* **2015**, *5*, 5008-5015.

[13] a) J. Kim, S. S. Stahl, *ACS Catal.* **2013**, *3*, 1652-1656; b) D. Damodara, R. Arundhathi, P. R. Likhar, *Adv. Synth. Catal.* **2014**, *356*, 189-198.

[14] a) K. C. Nicolau, C. J. N. Mathison, *Angew. Chem.* **2005**, *117*, 6146-6151; *Angew. Chem. Int. Ed.* **2005**, *44*, 5992-5997; b) J. Zhang, Z. Wang, Y. Wang, C. Wan, C. Wan, X. Zheng, Z. Wang, *Green Chem.* **2009**, *11*, 1973-1978; c) K. M. Lambert, J. M. Bobbitt, S. A. Eldirany, K. B. Wiberg, W. F. Bailey, *Org. Lett.* **2014**, *16*, 6484-6487; d) K. M. Lambert, J. M. Bobbitt, S. A. Eldirany, L. E. Kissane, R. K. Sheridan, Z. D. Stempel, F. H. Sternberg, W. F. Bailey, *Chem. Eur. J.* **2016**, *22*, 5156-5159.

[15] a) G.-W. Wang, *Chem. Soc. Rev.* **2013**, *42*, 7668-7700; b) R. S. Varma, *Green Chem.* **2014**, *16*, 2027-2041; c) T. K. Achar, S. Maiti, P. Mal, *RSC Adv.* **2014**, *4*, 12834-12839; I. Dokli, M. Gredicak, *Eur. J. Org. Chem.* **2015**, 2727-2732; d) S. L. James, C. J. Adams, C. Bolm, D. Braga, P. Collier, T. Friščić, F. Grepioni, K. D. M. Harris, G. Hyett, W. Jones, A. Krebs, J. Mack, L. Maini, A. G. Orpen, I. P. Parkin, W. C. Shearouse, J. W. Steed, D. C. Waddell, *Chem. Soc. Rev.* **2012**, *41*, 413-447; e) J. G. Hernández, C. Bolm, *J. Org. Chem.* **2017**, *82*, 4007-4019; f) J.-L. Do and Tomislav Friščić, *ACS Cent. Sci.* **2017**, *3*, 13-19.

[16] R. Mocci, L. De Luca, F. Delogu, A. Porcheddu, *Adv. Synth. Catal.* **2016**, *358*, 3135-3144.

[17] a) M. K. Beyer, H. Clausen-Schaumann, *Chem. Rev.* **2005**, *105*, 2921-2941; b) P. J. Walsh, H. Li, C. A. de Parrodi, *Chem. Rev.* **2007**, *107*, 2503-45; c)T. K. Achar, P. Mal, *J. Org. Chem.* **2015**, *80*, 666-672; d) L. Li, J.-J. Wang, G.-W. Wang, *J. Org. Chem.* **2016**, *81*, 5433-5439; e) L. Konnert, F. Lamaty, J. Martinez, E. Colacino, *J. Org. Chem.* **2014**, *79*, 4008-4017; f) Z.-J. Jiang, Z.-H. Li, J.-B. Yu, W.-K. Su, *J. Org. Chem.* **2016**, *81*, 10049-10055; g) V. Porte, M. Thioloy, T. Pigoux, T.-X. Metrò, J. Martinez, F. Lamaty, *Eur. J. Org. Chem.* **2016**, 3505-3508; h) T.-X. Metrò, J. Bonnamour, T. Reidon, A. Duprez, J. sarpoulet, J. Martinez, F. Lamaty, *Chem. Eur. J.* **2015**, *21*, 12787-12796; j) A. Beillard, X. Bantreil, T.-X. Mètro, J. Martinez, F. Lamaty, *New J. Chem.* **2017**, *41*, 1057-1063.

[18] a) R. Thorwirth, F. Bernhardt, A. Stolle, B. Ondruschka, J. Asghari, *Che. Eur. J.* **2010**, *16,* 13236-13242; b) I. Huskić, I. Halasz, T. Friščić, H.

Vančik ***Green Chem.*** **2012**,*14*, 1597-1600; c) G. Cravotto, E. C. Gaudino in *Ball Milling Towards Green Synthesis: Applications, Projects, Challenges,* (Eds.: A. Stolle, B. Ranu) Series RSC Green Chemistry; **2014**, pp. 58-80. d) R. Ghorbani-Vagheri, H. Veisi, *Synthesis*, 0945-0950.

[19] a) L. De Luca, G. Giacomelli, A. Porcheddu, *Org. Lett.* **2001**, *3*, 3041-3043; b) L. De Luca, G. Giacomelli, A. Porcheddu, *Org. Lett.* **2001**, *3*, 1519-1521; c) L. De Luca, G. Giacomelli, A. Porcheddu, *J. Org. Chem.* **2001**, *66*, 7907-7909; d) M. G. Mura, L. De Luca, M. Taddei, J. M. J. Williams, a. Porcheddu, *Org. Lett.* **2014**, *16*, 2586-2589.

[20] The principal advantages of using NCS include the ease in handling, the mild conditions under which chlorination proceeds, and the simplicity of removal of the innocuous by product succinimide.

[21] a) J. M. Antelo, F. Arce, J. Crugeiras, C. Pastoriza, A. Rios, *J. Chem. Research (S)* **2001**, 20-21; b) J. M. Antelo, F. Arce, J. Crugeiras, M. Parajò, *J. Phys. Org. Chem.* **1997**, *10*, 631-636; c) S. R. Rajamaki, L. De Luca, F. Capitta, A. Porcheddu, *RSC Adv.* **2016**, *6*, 38553-38557.

[22] The *N*-chlorobenzylimine **C** was used in separate reaction as starting material to prove the pathways leading to compounds **D** and **E**.

[23] A. Wang, H. Jiang, *J.Org. Chem.* **2010**, *75*, 2321-2326.

[24] P. Li, L. Wang, L. Zhang, G.-W. Wang, *Adv. Synth. Cat.* **2012**, *354*, 1307-1318.

[25] W. Han, B. Liu, J. Chen, Q. Zhou, *Synlett*. **2017,** *28*, 835-840.

[26] L. Gu, C. Jin, *Chem. Comm.* **2015**, *51*, 6572-6575.

[27] C. M. Nicklaus, P. H. Phua, T. Buntara, S. Noel, H. J. Heeres, J. G. de Vries, *Adv. Synth. Cat.* **2013**, *355*, 2839-2844.

[28] C.-P. Zhang, J. Cai, C.-B. Zhou, X.-P. Wang, X. Zheng, Y.-C. Gu, J.-C. Xiao, *Chem. Comm.* **2011**, *47*, 9516-9518.

[29] H. Huang, X. Li, C. Yu, Y. Zhang, P. S. Mariano, W. Wang, *Angew. Chem.* **2017***, 129,* 1522-1527*; Angew. Chem. Int. Ed.* **2017**, *56*, 1500-1505.

[30] E. Barragan, A. Bugarin, *J. Org. Chem.* **2017**, *82*, 1499-1506.

[31] S. H. Christensen, E. P. K. Olsen, J. Rosenbaum, R. Madsen, *Org. Biomol. Chem.* **2015**, *13*, 938-945.

[32] Q. Feng, Q. Song, *J. Org. Chem.* **2014**, *79*, 1867-1871.

[33] D. Leow, *Org. Lett.* **2014**, *16*, 5812-5815.

[34] S. Kamijo, K. Tao, G. Takao, H. Tonoda, T. Murafuji, *Org. Lett.* **2015**, *17*, 3326-3329.

[35] H. Jiang, J. R. Bak, F. J. Lopez-Delgado, K. A. Jorgensen, *Green Chem.* **2013**, *15*, 3355-3359.

[36] M. Iinuma, K. Moriyama, H. Togo, *Eur. J. Org. Chem.* **2014**, *2014*, 772-780.

[37] B. Skillinghaug, C. Sköld, J. Rydfjord, F. Svensson, M. Behrends, J. Sävmarker, P. J. R. Sjöberg, M. Larhed, *J. Org. Chem.* **2014**, *79*, 12018-12032.

[38] H. Niu, L. Lu, R. Shi, C. W. Chaing, A. Lei, *Chem. Commun*, **2017**, *53*, 1148-1151.

[39] G. Olivo, S. Giosia, A. Barbieri, O. Lanzalunga, S. Di Stefano, *Org. Biomol. Chem.* **2016**, *14*, 10630-10635.

[40] Y. Kumar, Y. Jaiswal, A. Kumar, *J. Org. Chem.* **2016**, *81*, 12247-12257.

[41] B. V. Rokade, S. K. Malekar, K. R. Prabhu, *Chem. Comm.* **2012**, *48*, 5506-5508.

[42] C. Tao, B. Wang, L. Sun, Z. Liu, Y. Zhai, X. Zhang, J. Wang, *Org. Biomol. Chem.* **2017**, *15*, 328-332.

[43] Q. Feng, Q. Song, *Adv. Synth. Cat.s* **2014**, *356*, 1697-1702.

[44] Y.-J. Zhuang, J. Liu, Y.-B. Kang, *Tetrahedron Lett.* **2016**, *57*, 5700-5702.

[45] L. Jia, X. Junchao, R. Jiangmeng, Z. Bu-Bing, *Chem. Lett.* **2014**, *43*, 190-192.

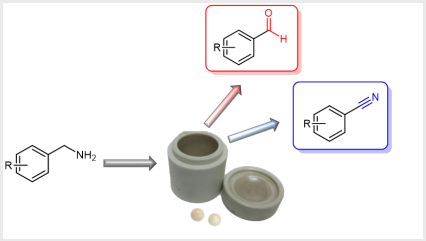
[46] R. Kupfer, U. H. Brinker, *J. Org. Chem.* **1996**, *61*, 4185-4186.

Entry for the Table of Contents (Please choose one layout)

Layout 1:

FULL PAPER

A mild, efficient, metal- and solvent-free oxidation of primary amines to aldehydes, ketones and nitriles under ball-milling conditions is presented. This method has proved to be compatible with various functional groups and requires easily accessible starting materials. Simple filtration of the reaction mixture through a pad of silica gel affords pure aldehydes, ketones and nitriles products.



Mechanochemical, oxidation, amine.

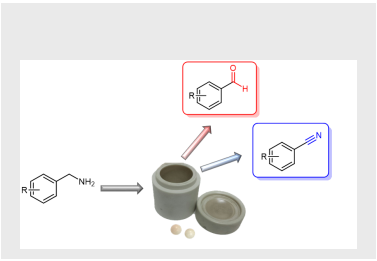
*Silvia Gaspa, Andrea Porcheddu, Antonio Valentoni, Sebastiano Garroni, Stefano Enzo and Lidia De Luca**

Page No. – Page No.

A Mechanochemical assisted oxidation of amines to carbonyl compounds and nitriles

Layout 2:

FULL PAPER



Mechanochemical, oxidation, amine.

*Silvia Gaspa, Andrea Porcheddu, Antonio Valentoni, Sebastiano Garroni, Stefano Enzo and Lidia De Luca**

Page No. – Page No.

A Mechanochemical assisted oxidation of amines to carbonyl compounds and nitriles

*