Green Chemistry

PAPER

View Article Online
View Journal | View Issue

Cite this: *Green Chem.*, 2022, **24**, 4859

Mechanochemical Fischer indolisation: an eco-friendly design for a timeless reaction†

Andrea Porcheddu, [a] Rita Mocci, *[a] Margherita Brindisi, *[b] Federico Cuccu, [a] Claudia Fattuoni, [a] Francesco Delogu, [c] Evelina Colacino [d] and Maria Valeria D'Auria [b]

Received 22nd February 2022,
Accepted 6th May 2022

DOI: 10.1039/d2gc00724j

rsc.li/greenchem

We developed an environmentally friendly mechanochemical protocol to induce an effective Fischer indolisation to synthesize indoles and indolines taking advantage of oxalic acid and dimethylurea. The solvent-free procedure shows versatility and wide scope; it applies to a broad range of arylhydrazines and carbonyl compounds, leading to variously decorated indoles and indolenines. Upon suitable modification, the methodology can also allow preparing compounds of pharmaceutical interest.

Introduction

Nitrogen-containing heterocycles have crucial importance in medicinal chemistry and drug discovery, as demonstrated by their striking predominance in marketed drugs.[1–4] Owing to their variety of biological activities, indole- and indoline-based structures have always deserved particular importance, being broadly found in medicinally relevant compounds of natural[5–8] and synthetic origins.[9–11]

The indole scaffold has been referred to as a "privileged scaffold"[12–14] owing to its capacity to interact with a diverse range of receptors, such as dopamine, serotonin and sigma receptors with high affinity.[15–18] Moreover, indole-based marketed drugs cover a broad set of indications, including anti-inflammatory, antihypertensive, anti-tumor, antiemetic, and antimigraine activities, among others (Fig. 1).[19]

Despite indole primacy within the family, indolenines and their reduced counterparts (*i.e.* indolines) also represent recurrent substructures inherently incorporated in numerous alkaloids as well as medicinally relevant compounds (Fig. 2).[20–26]

In general, the central relevance of this class of compounds significantly fostered synthetic research efforts towards the achievement of indole-based complex molecules and simpler architectures for medicinal chemistry applications.[27,28]

Fisher indolisation and its interrupted variation still represent the preeminent method for synthesizing the indole and indolenine cores, respectively (Scheme 1, pathways a and b). This timeless reaction was first discovered in 1883 by Emil Fischer and found a broad array of applications in industry and academia over the years.[29–34] Instead, an indolenine ring is generated in the case of α,α′-disubstituted aldehydes and ketones (namely, the interrupted Fischer variation, Scheme 1, pathway b).[29–32] The metastable indolenines quickly undergo 1,2-migration under acid conditions to give the thermodynamically more stable indole (Scheme 1, pathway c). This is a well-known phenomenon that readily occurs in indolenine chemistry.[33,34]

Effective generation of indole-based compounds employing Fischer reaction usually requires strong acids in organic solvents (toluene, xylene, DMF, THF, *etc.*) at elevated temperatures (up to 200 °C). Typical acidic catalysts used for Fischer-type reactions include Brønsted acids (HCl, H_2SO_4, TFA, *p*-TsOH,

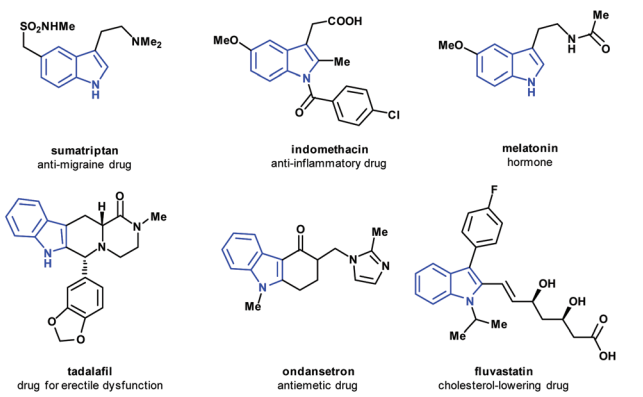


Fig. 1 Structures of indole-based marketed drugs.

[a]*Dipartimento di Scienze Chimiche e Geologiche, Università degli Studi di Cagliari, Cittadella Universitaria, 09042 Cagliari, Italy. E-mail: rita.mocci@unica.it*
[b]*Dipartimento di Farmacia, Università degli Studi di Napoli 'Federico II', Via Domenico Montesano 49, 80131 Napoli, Italy. E-mail: margherita.brindisi@unina.it*
[c]*Dipartimento di Ingegneria Meccanica, Chimica, e dei Materiali, Università degli Studi di Cagliari, via Marengo 2, 09123 Cagliari, Italy*
[d]*ICGM, Univ Montpellier CNRS, ENSCM, Montpellier, France*

† Electronic supplementary information (ESI) available. See DOI: https://doi.org/10.1039/d2gc00724j

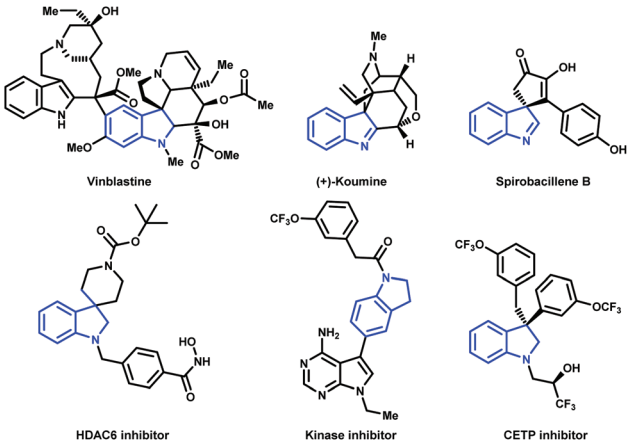


Fig. 2 Structures of indol(en)ine-containing alkaloids and another synthetic medicinally relevant compounds.

PPA, AcOH),[34–39] and Lewis acids (BF_3, $ZnCl_2$, $AlCl_3$, $TiCl_4$, PCl_3).[40–42]

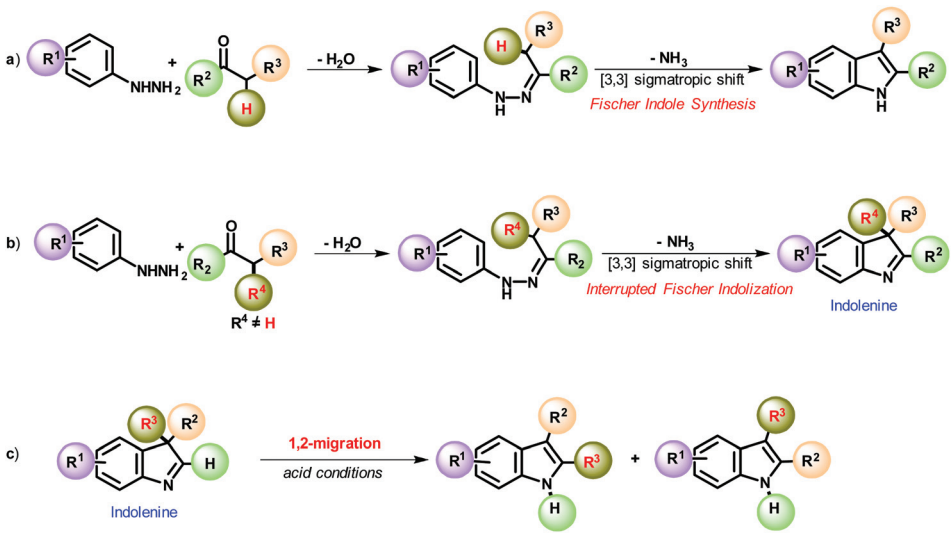
As a result, the Fischer indolisation is an energy-demanding process generating considerable waste, mainly because of the large amount of strong acid catalysts needed to boost the reaction towards the complete conversion of the reactants. Many of the reported methods suffer from drawbacks such as harsh or sensitive reaction conditions (ethyl diazoacetate, NIS, hazardous reagents: $Zn(CN)_2$, $BF_3{\cdot}OEt_2$, *N*-nitrosoanilines, vinyl azides) or limited substrate scope.[43–48]

Implementation of Fischer protocols in a greener and more sustainable mode has attracted significant attention in the past few years. Newly proposed methodologies have focused on heterogeneous and recyclable solid acid catalysts (*e.g.* zeolites, montmorillonite clays, amberlyst).[49–51] Still, their practical application is often anyway limited by restricted accessibility and/or rapid deactivation. The Fischer reaction was also developed in environmentally benign solvents such as ethanol and water.[35,52,53] However, the latter procedures are promoted by SO_3H-functionalized Brønsted acidic ionic liquids. The preparation of these imidazolium-based catalysts requires additional synthetic steps and strong acids (H_2SO_4, HCl, H_3PO_4 *etc.*, at water reflux) for the protonation of the final zwitterions, thus undermining the validity of the initial assumptions, and questioning about the sustainability of the process considering the toxicity of ionic liquids.[54,55] In addition, complete conversion is achieved at temperatures above 80 °C, which are often inconsistent with the use of *temperature-sensitive* functional substrates.

We herein report the results of our extensive experimentation aimed at developing a mechanochemical Fischer-type protocol of broad usefulness to synthesize indole derivatives. The mechanochemical approach is gaining increasing attention due to its ability of imparting existing methodologies with higher efficiency and sustainability.[56–67]

Among the advantages, mechanochemical activation helps circumventing the challenges associated with solvent selection and reagent solubility.[65,68,69] This aspect is particularly relevant when setting up 'greener' protocols and multistep sequences. Furthermore, reduced energy costs and minimum operator's exposure to chemicals render the process more cost-effective.[56,58,70] In this context, implementing a sustainable mechanochemical Fisher indolisation protocol prone to broad application shows undeniable appeal.

A recently published article[71] on the Fischer indole synthesis by mechanochemical activation highlights the relevance of this topic and the usefulness of ball-milling to ensure more sustainable access to this class of compounds. However, despite the significant improvement, this procedure still has some shortcomings that severely limit its utility. In particular,



Scheme 1 General Fischer indole synthesis (pathway a) and its interrupted variation (pathway b). Acid promoted 1,2-alkyl migration of 3,3′ alkylindolenine (pathway c).

the scope of this newly developed methodology is limited to the preparation of tetrahydrocarbazole frameworks in the presence of silica as a grinding additive (720 mg $mmol^{-1}$ of ketone).

We started our investigation on the mechanochemical Fischer synthesis prompted by the need for wide-scope, operationally eco-compatible and straightforward protocols. *p*-Tolylhydrazine hydrochloride **1a** and propiophenone **2a** were selected as the model substrates to set up the appropriate conditions for developing a more comprehensive strategy for the adequate preparation of indole- and indoline-based templates (Table 1).

Aldehydes and ketones are predominantly liquid, so the reaction needs a solid grinding auxiliary/adsorbent to be performed effectively. Initially, we reasoned that silica gel could be the best choice since it was already successfully used for the mechanosynthesis of tetrahydrocarbazole derivatives. Related experiments have been performed in ZrO_2 jars (15 mL) with two balls (∅ = 8 mm, m_{tot}: 6.5 g), where *p*-tolylhydrazine hydrochloride **1a** (159 mg, 1.0 mmol) and propiophenone **2a** (147 mg, 1.1 mmol) were ball-milled in the presence of silica (300 mg) with a mixer mill (30 Hz) for 100 minutes.

Under these conditions, as previously highlighted,[71,72] silica becomes an even stronger solid acid by absorbing HCl on its surface, thus promoting the subsequent acid-catalyzed Fischer reaction. To our surprise, in these first attempts to promote the indolisation of *in situ* generated hydrazone **4a**,[73] we detected only the formation of small amounts of the desired indole **3a** accompanied by the unreacted ketone **2a** (Table 1, entry 1, **3a : 4a** = 99 : 1).

At this point, knowing that Fischer indole synthesis is an acid promoted reaction, we increased the acidity of the resulting solid mixture by adding $NaHSO_4$ (120 mg) to promote the [3 + 3] sigmatropic rearrangement under ball-milling conditions (Table 1, entry 2).[74] The increased acidity resulted in a significant rise in indole yield (46%),[75–77] highlighting that the operating acidity of the reactive medium is a crucial design parameter controlling the mechanochemical hydrazone-indole conversion. This result prompted us to increase the ratio of the sulfate acid salt relating to silica gel. However, this was detrimental on the indolisation process (Table 1, entry 3).

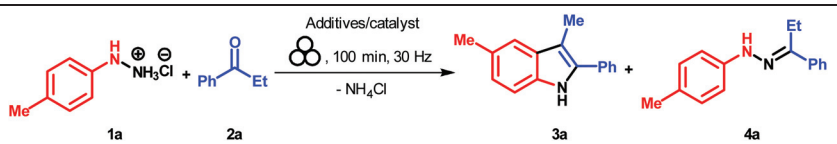
We observed similar outcomes by adding a catalytic amount of solvent (MeOH, CH_3CN; LAG, η = 0.1 μL mg^{-1}; Table 1, entries 4 and 5). On the other hand, $NaHSO_4$ (120 mg) in the absence of silica gel did not promote the transformation denoting a synergistic effect of the two components (Table 1, entry 6). Under these reaction conditions, even extending the milling time (300 min) did not significantly improve the result. Since acid catalysis proved crucial for boosting reaction, we turned our attention to other solid acids such as tetrabutylammonium bisulfate, *p*-toluensulfonic acid (PTSA), and tartaric acid (Table 2 and Table S1 in ESI†). However, they showed modest efficiency in promoting the Fischer indole synthesis, thus providing indole **3a** in low yields.

Assuming that the inefficient formation of phenylhydrazone **4a** is a consequence of our working conditions, we decided to use a basic scavenger for hydrochloric acid, thus favoring the nucleophilic attack from the acid-free phenylhydrazine.

In this regard, previous work[78] has proven that imidazole can act as a mild base, allowing to overcome drawbacks related to the low conversion of the reagents into phenylhydrazone **4a**. Imidazole was very effective in promoting the complete formation of phenylhydrazone **4a**; on the contrary, it significantly inhibited the subsequent [3 + 3] rearrangement to the indole ring (Table 2, entry 4).

The indolisation process was split in two distinct steps to fine-tune the reaction parameters. The first one was targeting the formation of phenylhydrazone **4a** in the presence of imidazole, while in the second, PTSA (2 equiv.) was added to the same jar to promote indole ring generation. However, even in this case, only small amounts of the desired indole **3a** were obtained, accompanied by a considerable percentage of unreacted starting materials and the simultaneous formation of aniline as a side-product (Table 2, entry 5). Such a result suggested the occurrence of a competing path arising from the

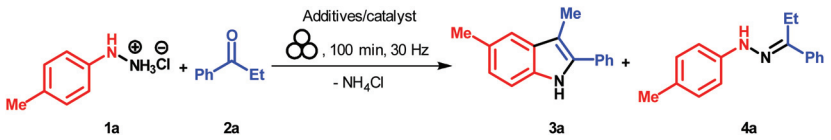
Table 1 Screening of reaction conditions for the mechanochemical Fischer indole synthesis[a,b]



Entry	Additive (mg)	Acid (mg)	**3a**[c] (%)
1	SiO_2 (300)	—	14
2	**SiO_2 (300)**	**$NaHSO_4$ (120)**	**46**
3	SiO_2 (150)	$NaHSO_4$ (120)	20
4[d]	SiO_2 (300)	$NaHSO_4$ (120)	34
5[e]	SiO_2 (300)	$NaHSO_4$ (120)	35
6	—	$NaHSO_4$ (120)	—

[a] **1a** (158.6 mg, 1.0 mmol), **2a** (147.6 mg, 1.1 mmol) and additive were ball-milled in a 15 mL ZrO_2 milling jar with 2 milling balls (∅ = 8 mm, m_{tot} = 6.5 g overall) of the same material. [b] Selectivity ratio **3a : 4a** >99%. [c] Determined by GC-MS analysis. [d] Catalytic amounts of MeOH were used (η = 0.1 μL mg^{-1}). [e] Catalytic amounts of CH_3CN were used (η = 0.1 μL mg^{-1}).

Table 2 Screening of reaction conditions for the mechanochemical Fischer indole synthesis



Entry[a]	Catalysts (mmol)	3a[b] (%)	Ratio[b] (%) of 3a : 4a
1	PTSA (1.5)	36	99 : 1
2	OA (1.5)	32	99 : 1
3	Tartaric acid (1.5)	6	1 : 99
4	Imidazole (1)	—	1 : 99
5[c]	PTSA/imidazole (2 : 1)	25	78 : 22
6	DMU/PTSA (7 : 3)	43	77 : 23
7	DMU/OA (7 : 3)	40	71 : 29
8[d]	DMU/OA (7 : 3)	56	69 : 31
9[d,e]	DMU/OA (7 : 3)	50	73 : 27
10[d,e]	DMU/OA (3 : 7)	58	99 : 1
11[d]	DMU/OA (1.5 : 3.5)	60	99 : 1
12[d,e]	DMU/OA (1.5 : 3.5)	68	99 : 1
13[d,e]	DMU/OA (1.5 : 3.5), MeOH (η = 0.1 μL mg^{-1})	55	99 : 1
14[d,e]	**DMU/OA (1.5 : 3.5), CH_3COOH (η = 0.1 μL mg^{-1})**	**76**	**99 : 1**
15[d,e]	DMU/OA (1.5 : 3.5), 3-pentanol (η = 0.1 μL mg^{-1})	77	99 : 1
16[d,e]	DMU/OA (1.5 : 3.5), DMF (η = 0.1 μL mg^{-1})	79	99 : 1

[a] **1a** (158.6 mg, 1.0 mmol), **2a** (147.6 mg, 1.1 mmol), and catalysts were ball-milled in a 15 mL ZrO_2 milling jar with 2 milling balls (∅ = 8 mm, 6.5 g overall) of the same material. [b] Determined by GC-MS. [c] **1a** (158.6 mg, 1.0 mmol), **2a** (147.6 mg, 1.1 mmol) and imidazole (68.1 mg, 1.0 mmol) were milled for 60 minutes, afterward PTSA (344.4 mg, 2.0 mmol) was added, and the mixture was ball-milled for additional 100 minutes. [d] The jar was loaded with ZrO_2 balls (20, ∅ = 3 mm, m_{tot} = 6.5 g). [e] The mixture was ball milled for 300 minutes.

cleavage of the *N–N* phenylhydrazine bond under our working conditions. At this stage, we envisioned the possibility of screening different binary mixtures of hydrogen bond acceptors and donors, wondering if such a mixture, under mechanochemical processing conditions, could act as an efficient catalyst for the Fischer indolisation (see Table 2 and Table S1 in ESI†).

Gratifyingly, the oxalic acid (OA) and dimethylurea (DMU) mixture revealed remarkable efficiency. Indeed, OA displays marked acidity that could be beneficial in promoting the Fischer reaction (Table 2, entries 6 and 7). Regarding DMU, its presence significantly increased the conversion rate, while playing a minor role in the process selectivity.

In these first studies, the mechanochemical processes were carried out in the presence of an excess of the two solid components, specifically DMU (7 equiv., 617 mg) and OA (3 equiv., 270 mg).[39]

Moreover, it was observed a slight increment in the efficacy of the process, switching from 2 (∅ = 8 mm) to 20 (∅ = 3 mm) zirconia balls, keeping the overall final weight unchanged (m_{tot}: 6.5 g, Table 2, entry 8).

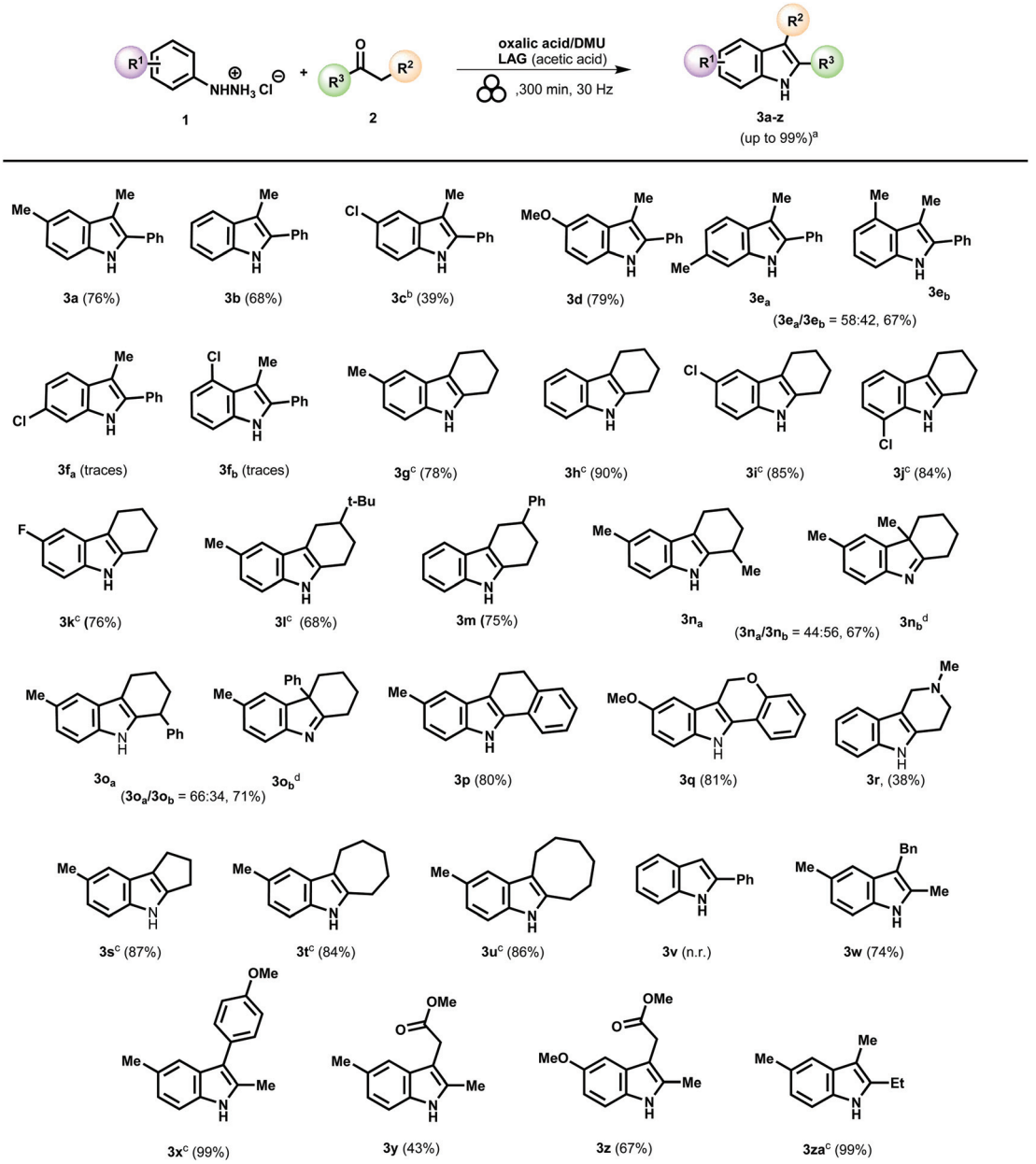
These reaction conditions proved valuable in the mechanochemical Fischer indole synthesis, with the desired indole **3a** obtained in 56% of yield after 100 minutes of milling (Table 2, entry 8).

An increase in reaction time up to 250 minutes did not significantly improve the results in terms of reaction yields (Table 2, entry 9). In contrast, a change in the ratio composition of DMU and OA resulted in an increased selectivity (99 : 1, Table 2 entry 10). Additionally, comparable results were obtained halving the amount of auxiliary grinding mixture (DMU and OA), thus reducing the reaction waste (Table 2, entry 11). Under these reaction conditions, we observed that ball milling over longer times enhanced conversion without affecting the process selectivity (Table 2, entry 12).

The procedure performed even better under liquid-assisted grinding conditions, in the presence of a small amount of solvent (η = 0.1, μL mg^{-1}). We observed that higher boiling point solvents provided indole **3a** with improved and comparable yields (Table 2, entries 14–16). However, for the scope of this procedure, we identified acetic acid as the most suitable additive, offering a good balance between efficacy, cost of production, and environmental impact. Moreover, acetic acid can be easily removed during the final purification step. Once the reaction was accomplished, the crude was indeed purified by trituration with water. Indole **3a** was recovered by filtration without using a single drop of organic solvent, emphasizing the green character of this mechanochemical protocol.

Once identified the optimal conditions, the reaction scope was broadened by reacting a set of different phenylhydrazines **1a–1i** and **5a** and ketones **2a–2q** (as specified in the ESI†), in order to validate the generality and efficiency of this mechanochemical protocol. The results were mostly consistent with the general trend observed for the Fischer indole synthesis in solution, which is considerably influenced by the steric and electronic nature of the substituent groups (Scheme 2).

Going into more detail about the structure–reactivity relationship, we observed that 4-methyl- and phenylhydrazine provided indoles **3a** and **3b**, respectively, in comparable amounts (Scheme 2). However, introducing a chlorine substi-



Scheme 2 Reaction Scope of Mechanochemical Fischer indole synthesis. Reaction conditions: **1** (1 mmol), **2** (1.1 mmol), oxalic acid (3.5 mmol), dimethylurea (1.5 mmol) and acetic acid (η = 0.1 μL mg^{-1}) were ball-milled in a 15 mL ZrO_2 milling jar with 20 milling balls (∅ = 3 mm, m_{tot} 6.5 g) of the same material for the given time. [a] Isolated yields. [b] The reaction mixture was ball milled for 400 minutes. [c] The reaction mixture was ball milled for 100 minutes. [d] Isomer ratio determined after reduction, assuming a completed conversion of indolenine into the corresponding indoline. n.r. = no results.

tuent on the *para* position of the aromatic ring in the phenylhydrazine generally has a detrimental effect on the reaction outcome (Scheme 2, indole **3c**). Low conversion of phenylhydrazone to the indole **3c** was observed even after prolonged reaction time (400 minutes). Conversely, the reaction of 4-methoxy phenylhydrazine with the propiophenone proceeded more slightly, providing the corresponding indole in 79% yield (Scheme 2, indole **3d**).

Then, the reactivity of *meta*-substituted phenylhydrazines was explored to investigate whether a possible effect on the selectivity could be detected. In solution, *meta*-substituted phenylhydrazines usually give a mixture of 4- and 6-substituted indoles. However, the relative amounts vary to only a slight degree based on the electronic nature of the substituents, being the 6-substituted indole the leading product in the presence of an electron-donating group and the 4-substituted indole with an electron-withdrawing group.[79]

According to this general trend, the ball milling of 3-methylphenylhydrazine with propiophenone gave a mixture of two regioisomers showing modest regioselectivity for the

indole **3e$_a$** (**3e$_a$**/**3e$_b$**: 58/42, Scheme 2). On the other hand, 4- and 6-substituted chloro derivatives **3f$_a$** and **3f$_b$** were detected only in traces.

Subsequently, we focused on preparing an array of tetrahydrocarbazole products using as starting carbonyl components symmetric cyclic aliphatic ketones.

The optimized process conditions afforded tetrahydrocarbazoles **3g–o$_a$** in high yields and purity (Scheme 2). In this case, the presence of halogen-substituents on the aromatic ring was compelling and well-tolerated (entries **3i-k**). Moreover, the presence of bulky or pendant (phenyl) groups on the cyclohexanone ring did not appear to dramatically perturb the performance of this Fischer indole synthesis (Scheme 2, indoles **3l** and **3m**). The investigation was next extended to the reaction between 2-substituted cyclohexanone and 4-methylphenylhydrazine (Scheme 2).

Previous studies[79,80] in solution revealed that the selectivity of the process was influenced by both the nature of the acid catalyst and the electronic and steric properties of the 2-substituent, driving the reaction toward the preferential formation of the indole product (*i.e.*, **3n$_a$**) and/or the alternative indolenine **3n$_b$**, (Scheme 2). Usually, when the process is performed in the presence of glacial acetic acid, the indolenine derivative **3n$_b$** results in the major component. In contrast, under strongly acidic conditions, such as aqueous sulfuric acid, the formation of the less substituted ene-hydrazine is favored, leading to the preferential formation of the corresponding indole **3n$_a$**. In addition, the nature of the substituents on the carbon in α-position to the carbonyl group significantly affects the regioselectivity.[79,80] Under the optimized mechanochemical conditions, we examined the behavior of two cyclohexanone derivatives bearing a pendant at the alpha position, namely 2-methyl- and 2-phenyl-cyclohexanone.

Furthermore, to avoid any possible decomposition of the indolenine during the purification steps, after the completion of the conversion of the ketone to indolenine **3n$_b$**, **3o$_b$** or indole **3n$_a$**, **3o$_a$**, the reaction mixture was reduced *in situ* (see ESI,† and Scheme 4), resulting in the transformation of the indolenine to the corresponding indoline. In the case of the 2-methyl cyclohexanone, the reaction led to a mixture of two possible products with a slight preference for the indolenine **3n$_b$** (Scheme 2, **3n$_a$** : **3n$_b$** = 44 : 56), in line with previous studies in solution.[79] The ratio indole/indolenine was reversed by using 2-phenyl-cyclohexanone. The presence of a phenyl group in the α-position to the carbonyl group favors the formation of the indole **3o$_a$** over the indolenine **3o$_b$** (Scheme 2, **3o$_a$** : **3o$_b$** = 66 : 34, Scheme 2).

A constrained cyclohexanone system, such as the α-tetralone **2e**, was subjected to the reaction conditions leading to the corresponding indole (**3p**) in high yield (Scheme 2). At the same time, the cromanone **2l** was coupled with 4-methoxy-phenylhydrazine providing the corresponding indole **3q** in a very satisfying yield (Scheme 2). Remarkably, the present methodology was successfully applied to the synthesis of the indole **3r** which represent a crucial precursor for the synthesis of Tubastatin A, a selective HDAC6 inhibitor.[81]

To examine the ring size effect of cyclic ketones, cyclopentanone, cycloheptanone, and cyclooctanone were milled in the presence of 4-methylphenylhydrazine, resulting in the target indoles **3s–3u**, in good to excellent yields. The mechanochemical Fischer indole synthesis, performed using non-symmetric methyl ketone substrates, represents another interesting example of a substrate-controlled regioisomeric reaction.

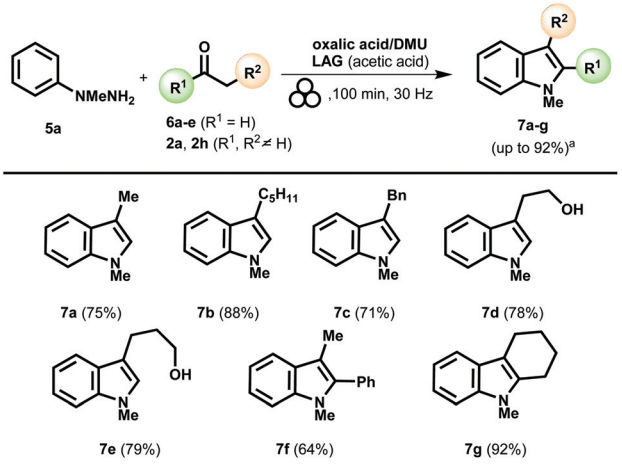
Unfortunately, when acetophenone was submitted to the reaction conditions, the corresponding 2-phenylindole was detectable not even in trace amounts and after prolonged reaction time (Scheme 2, indole **3v**). Although this may appear a significant limitation of our mechanochemical protocol, it has been exploited to selectively synthesize a series of 2-methyl indoles (Scheme 2: **3w–z**). For example, the reaction of phenylhydrazine **1a** with methyl ketones **2o** and **2p** (Table S2 in ESI†) gave only one of two possible regioisomers, affording the indoles nucleus decorated with a benzyl or a *p*-methoxy-phenyl pendant in 3-position in 74 and 99% isolated yields, respectively (Scheme 2, indoles **3w** and **3x**). Furthermore, the procedure proved to be compatible with the ester moiety, providing both the indoles **3y** and **3z** in 43% and 67% yields and opening a way for further derivatization through the carboxylic function (Scheme 2).

Finally, when a symmetric ketone with a linear alkyl chain was used, the indolisation proceeded smoothly (Scheme 2, indole **3za**). In general, the developed mechanochemical protocol provided good results, in terms of yields and selectivity, for preparing indoles **3a–3za**.

At this point, we addressed our effort toward the synthesis of 2-unsubstituted indoles starting from the corresponding aldehydes. The previously optimized mechanochemical protocol was extended to a set of different aldehydes, such as propionaldehyde, 3-phenyl-propionaldehyde, and heptanal in the presence of the *p*-tolylhydrazine **1a**. Unfortunately, in all the experiments, the reaction provided a complex mixture from which it has not been possible to isolate the desired product. This issue could be overcome by adopting 1-methyl-1-phenylhydrazine **5a** (Scheme 3). A methyl substituent on the nitrogen atom (**N1**) played a crucial role in the process, allowing for **7a–7e** indole products (Scheme 3). Besides, indole derivatives **7f** and **7g**, using propiophenone and cyclohexanone, respectively, were successfully prepared (Scheme 3).

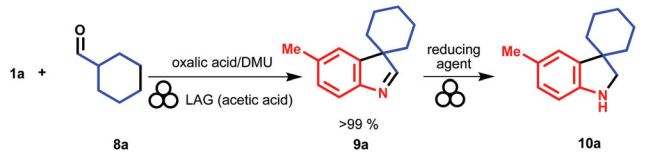
As stated in the introduction, the indolenine/indoline core is highly relevant for constructing biologically active compounds. Despite several reports on eco-friendly Fisher indole syntheses, sporadic investigations have been performed on its interrupted variation.[82,83] This is especially true for 3,3′-disubstituted indolenine frameworks associated with additional challenges.

Interrupted Fischer indolisation is still the most widely used approach to prepare the indolenine nucleus. However, as a rule, the synthesis of this heterocycle is developed in acetic acid, which plays the dual role of solvent and acid catalyst, needed to promote ring closure. The reaction requires an input of heat from an external source (>80 °C), and often the same experimental conditions needed to trigger the inter-



Scheme 3 Reaction scope of mechanochemical Fischer indole synthesis using *N*-methylphenylhydrazine. Reaction conditions: **5a** (1.0 mmol), **6** and **2** (1.1 mmol), oxalic acid (3.5 mmol), dimethylurea (1.5 mmol) and acetic acid (η = 0.1 μL mg^{-1}) were ball-milled in a 15 mL ZrO_2 milling jar with 20 milling balls (∅ = 3 mm, m_{tot} = 6.5 g) of the same material for the given time. [a] Isolated yields.

Table 3 Screening conditions for the mechanochemical synthesis of indolines



Entry[a]	Reducing agent	Equiv.	10[b]
1[c]	Pd/NH_4HCOOH	5 (mol%)/3	n.r.
2	$NaBH(OAc)_3$		n.r.
3	$NaBH_4$	4	90%
4	**$NaBH_4$**	**2**	**91%**
5	$NaBH_4$	1	50%
6[d]	$NaBH_4$	1.5	90%
7[d]	$NaBH_4$	1	70%

[a] **1a** (158.6 mg, 1 mmol), **8a** (123.4 mg, 1.1 mmol), oxalic acid (315.10 mg, 3.5 mmol), dimethylurea (132.16 mg, 1.5 mmol) and acetic acid (η = 0.1 μL mg^{-1}) were ball-milled in a 15 mL ZrO_2 milling jar with 20 milling balls (∅ = 3 mm, m_{tot} = 6.5 g) of the same material for 100 minutes, afterwards the jar was opened, the reducing agent was added and the reaction mixture was ball-milled for additional 60 minutes. [b] Determined by GC-MS. [c] The reaction mixture was ball milled in the presence of SiO_2 (175 mg) and MeOH (η = 0.25 μL mg^{-1}). [d] The reaction was performed in the presence of 3-pentanol instead of acetic acid (η = 0.1 μL mg^{-1}).

rupted Fischer indolisation promote the migration of one of the two side chains on the 3,3′-disubstituted indolenines, which generates the most thermodynamically stable indole ring (Scheme 1, pathway C).[34,84,85] Moreover, the acetic acid, used as a solvent in the synthesis of the indolenine core, is often incompatible with the reducing agents used in the next step to reduce the indolenines to indolines and, therefore, has to be distilled away. Solvent removal is energy demanding and could be a significant obstacle, mainly working at larger scale.

As extensively emphasized in the literature, working in this context is challenging. Finding innovative solutions that are entirely in line with the requirements of green chemistry becomes a complex puzzle hard to solve. Removing the solvent and working at room temperature are, at least from a theoretical point of view, the most straightforward solution to overcome the issues, combining the requirements of synthesis with those of green chemistry.

Once again, mechanochemistry is emerging as a green technology that can provide the right solutions to these complex problems, avoiding the propensity of the metastable indolenines to undergo 1,2-migration. For this reason, we decided to explore the feasibility of a Fischer interrupted reaction followed by the *in situ* reduction of the resulting indolenine and spiroindolenine.

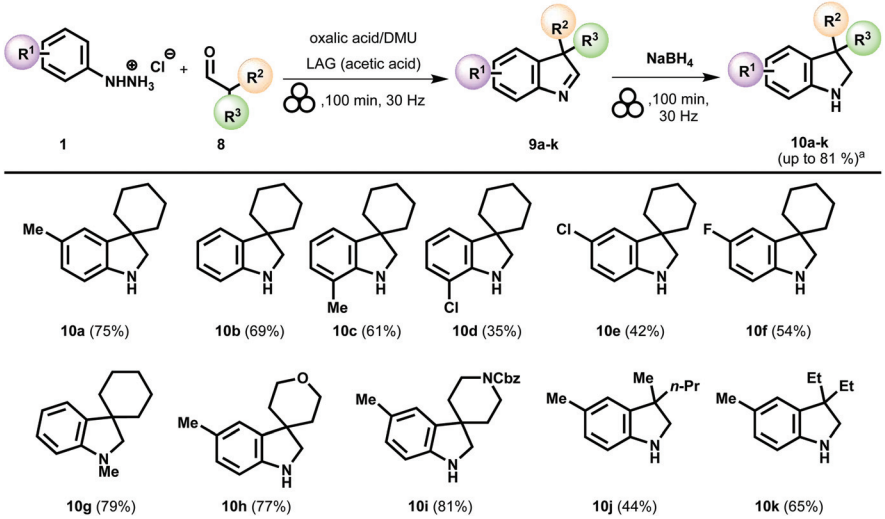
At first, we established the feasibility of the indolenine formation by reacting the 4-methyl-phenyl hydrazine and cyclohexane carboxaldehyde under the optimized reaction conditions. Then, we were pleased to observe an almost quantitative formation of the indolenine nucleus (Table 3, compound **9a**) by GC-MS and ^{1}H-NMR analysis on the reaction crude. Remarkably, the interrupted Fischer indolisation reaction proceeds smoothly using commercially available arylhydrazine hydrochlorides, which directly react *in situ* without any preliminary acid–base treatments to afford free hydrazine derivatives.

In addition, the desired indolenine was obtained selectively concerning the 1,2-migration product under the developed conditions. Based on previous reports on hydrogenation reactions under mechanochemical processing conditions,[86] the *in situ* reduction of the C=N double bond in the indolenine core was attempted. Our efforts to obtain the product using Pd catalyst and ammonium formate under transfer hydrogenation conditions led to a mixture of unidentified products (Table 3, entry 1).[87] Moreover, when $NaBH(OAc)_3$ was used, no conversion was observed (Table 3, entry 2). On the other hand, excellent results were achieved in the presence of 4 equivalents of $NaBH_4$ (Table 3, entry 3).

Finally, halving the amount of the reducing agent (2 matches) allowed complete conversion toward the desired product **10a** (Table 3, compare entries 4 and 5).

Interestingly, 3-pentanol (LAG, η = 0.1 μL mg^{-1}) allows to decrease the amount of sodium borohydride required to complete the reduction down to 1.5 equivalents (Table 3, compare entries 4 and 6). Nevertheless, green metrics based on the use of 3-pentanol did not show a significant improvement on the overall greenness of the methodology (see ESI, Scheme S4†). According to the above considerations, we adopted once again the acetic acid as liquid assistant of grinding.

The scope of the reaction was studied, and the strategy showed to be effective for a variety of 2-disubstituted aldehydes (Scheme 4, indolines **10a–10k**). Indoline derivative **10a** was isolated in 75% yield over two reaction steps by a short pad of silica gel. Reasonably good results were obtained using the



Scheme 4 Reaction Scope of Mechanochemical interrupted Fischer indole synthesis. Reaction conditions: **1** (1.0 mmol), **8** (1.1 mmol), oxalic acid (3.5 mmol), dimethylurea (1.5 mmol) and acetic acid (η = 0.1 μL mg^{-1}) were ball-milled in a 15 mL ZrO_2 milling jar with 20 milling ball (∅ = 3 mm, m_{tot} 6.5 g) of the same material for the given time. Afterwards, the jar was opened, the sodium borohydride (2.0 mmol) was added to the resulting reaction mixture that was further ball-milled for 60 minutes. [a] Isolated yields.

Table 4 Comparison of solution and mechanochemical protocols for the Fischer synthesis of indoles and indolines

	In solution[a]		Mechanochemistry	
Compound	*E*-Factor	Eco-scale	*E*-Factor	Eco-scale
3h	79.9	64.0	42.9	74.0
10b	278.4	45.0	214.3	52.5

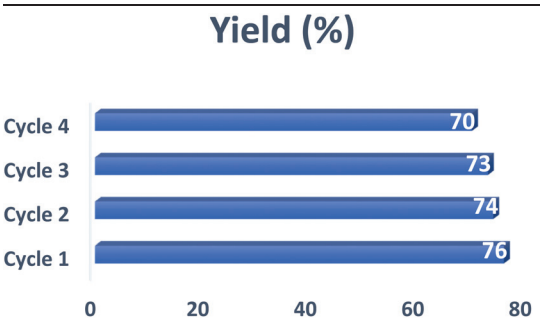
[a] For the Fischer and interrupted Fischer synthesis of indoles and indolines (in solution), two representative procedures were chosen for comparison: (i) in the presence of acidic clay as the catalyst for the indole compounds,[51] (ii)using acetic acid and sodium triacetoxyborohydride as a reducing agent for the synthesis of indolines.[85]

unsubstituted phenylhydrazine (Scheme 4, indoline **10b**). In this case, halogens-functionalized phenylhydrazine proved to be a more challenging substrate even though the reaction proceeded significantly (Scheme 4, indolines **10d–10f**). However, an outstanding outcome could be performed when using the 1-methyl-1-phenylhydrazine (Scheme 4, indoline **10g**). Finally, 2,2-disubstituted aldehyde derivatives bearing a heteroatom as a part of the ring were well tolerated. More specifically, reacting 4-formyltetrahydropyran with 4-methyl-phenylhydrazine led to indoline derivative **10h** in 77% yield. Besides, it was possible to efficiently prepare the indoline derivative **10i** with a Cbz-protected nitrogen atom in high yield (Scheme 4, 81% yield). Similar responses were recorded using the racemic 2-methylpentanal (Scheme 4, indoline **10j**, 44%) and 2-ethylbutanal (Scheme 4, indoline **10k**) as carbonylic partners.

Finally, green metrics were calculated to assess the environmental impact, effectiveness, and sustainability of the developed procedures (Table 4, for details, see the ESI†). The evaluation of the findings reported in the table pointed out and further demonstrated the advantages provided by the mechanochemical promoted Fischer (and interrupted Fischer) process, both in terms of *E*-factor[88–90] and Eco scale[91] values. Going beyond the interesting numerical results of the green metrics, it is worth emphasizing that this procedure does not require heating and proceeds at room temperature, preventing any potential degradation of heat-labile compounds. The provided methodology allowed to avoid using large amounts of liquid acids, replaced by the easy-to-handle solid mixture. This feature is also beneficial in terms of the purification steps, which are remarkably simplified since there is no need for solvent switching in the different reaction stages and the OA-DMU mixture can be removed by water treatment.

Finally, we have investigated the recycling of solid mixture containing OA and DMU in order to improve the environmental performance of the whole process. The experiments

Table 5 Grinding additive recycling[a]



[a] Reaction conditions: **1a** (1.0 mmol), **2a** (1.1 mmol) and acetic acid (η = 0.1 μL mg^{-1}) were ball-milled with the recycled mixture in a 15 mL ZrO_2 milling jar with 20 milling balls (∅ = 3 mm, m_{tot} = 6.5 g) of the same material for the given time.

carried out on the model reaction highlighted that the recycled solid grinding components could be used four times, maintaining their efficiency (Table 5). However, it is worth pointing out that the water's evaporation is a high energy demand process that should be accurately assessed concerning the actual advantages provided by the recycling steps.

Conclusions

In summary, we developed an effective mechanochemical protocol for generating a wide variety of indole- and indoline-based templates in short times and with high yield using a mixture of solid oxalic acid and dimethylurea. The number of examples and the variability of the nature of aldehydes, ketones and phenylhydrazines successfully converted demonstrated the broad scope and utility of the proposed method. Moreover, the newly developed protocol displays the potential to turn it into a practical coupling point for additional modification leading to compounds of pharmaceutical interest.

Author contributions

A. P. conceptualization, data curation, manuscript editing; R. M.: conceptualization and initial draft preparation; M. B.: conceptualization and initial draft preparation; E. C. data curation and manuscript editing; FC: experimental data analysis. C. F.: GC-MS analysis, manuscript editing; F. D.: manuscript editing and funding; M. V. D. supervision, manuscript editing, funding.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was supported by MIUR Italy PRIN 2017 project (2017A95NCJ) "Stolen molecules—Stealing natural products from the depot and reselling them as new drug candidate". M. B. and M. V. D. would like to thank the Department of Excellence of Pharmacy (2018–2022), University of Naples Federico II. The MIUR National Project PRIN "MultIFunctional poLymer cOmposites based on groWn matERials (MIFLOWER)" (grant number: 2017B7MMJ5_001) is kindly acknowledged. This work is a contribution to the COST Action CA18112[92–94] supported by COST (European Cooperation on Science and Technology).[95] COST (European Cooperation in Science and Technology) is a funding agency for research and innovation networks. Our Actions help connect research initiatives across Europe and enable scientists to grow their ideas by sharing them with their peers. This boosts their research, career and innovation. E.C. is grateful to Région Occitanie (France) for the Pre-Maturation 2020 – MECH-API grant (ESR_PREMAT – 00262).

Notes and references

1 E. Vitaku, D. T. Smith and J. T. Njardarson, *J. Med. Chem.*, 2014, **57**, 10257–10274.
2 N. Kerru, L. Gummidi, S. Maddila, K. K. Gangu and S. B. Jonnalagadda, *Molecules*, 2020, **25**, 1909.
3 M. M. Heravi and V. Zadsirjan, *RSC Adv.*, 2020, **10**, 44247–44311.
4 A. Mermer, T. Keles and Y. Sirin, *Bioorg. Chem.*, 2021, **114**, 105076.
5 A. W. Schammel, G. Chiou and N. K. Garg, *Org. Lett.*, 2012, **14**, 4556–4559.
6 L. Zu, B. W. Boal and N. K. Garg, *J. Am. Chem. Soc.*, 2011, **133**, 8877–8879.
7 A. Nishida, R. Tsuji and M. Nakagawa, *Heterocycles*, 2002, **58**, 587–593.
8 J. H. Rigby and S. Sidique, *Org. Lett.*, 2007, **9**, 1219–1221.
9 S. Dadashpour and S. Emami, *Eur. J. Med. Chem.*, 2018, **150**, 9–29.
10 A. Thakur, A. Singh, N. Kaur, R. Ojha and K. Nepali, *Bioorg. Chem.*, 2020, **94**, 103436.
11 Y. Li, Y. Xiong, G. Zhang, L. Zhang, W. Yang, J. Yang, L. Huang, Z. Qiao, Z. Miao, G. Lin, Q. Sun, T. Niu, L. Chen, D. Niu, L. Li and S. Yang, *J. Med. Chem.*, 2018, **61**, 11398–11414.
12 S. Oh, G. W. Go, E. Mylonakis and Y. Kim, *J. Appl. Microbiol.*, 2012, **113**, 622–628.
13 S.-F. Fu, J.-Y. Wei, H.-W. Chen, Y.-Y. Liu, H.-Y. Lu and J.-Y. Chou, *Plant Signaling Behav.*, 2015, **10**, e1048052.
14 Indoles are among the most critical bioactive heterocyclic structures, naturally present in tryptophan and the related neurotransmitter serotonin. Indole alkaloids also represent one of the largest classes of nitrogen-containing secondary metabolites, containing indole and/or indoline substructures. They are widely found in plants, bacteria, fungi and animals.
15 A. Kumari and R. K. Singh, *Bioorg. Chem.*, 2019, **89**, 103021.
16 T. V. Sravanthi and S. L. Manju, *Eur. J. Pharm. Sci.*, 2016, **91**, 1–10.
17 V. Sharma, P. Kumar and D. Pathak, *J. Heterocycl. Chem.*, 2010, 491–502.
18 S. Lal and T. J. Snape, *Curr. Med. Chem.*, 2012, **19**, 4828–4837.
19 N. Chadha and O. Silakari, *Eur. J. Med. Chem.*, 2017, **134**, 159–184.
20 M. Brindisi, J. Senger, C. Cavella, A. Grillo, G. Chemi, S. Gemma, D. M. Cucinella, S. Lamponi, F. Sarno, C. Iside, A. Nebbioso, E. Novellino, T. B. Shaik, C. Romier, D. Herp, M. Jung, S. Butini, G. Campiani, L. Altucci and S. Brogi, *Eur. J. Med. Chem.*, 2018, **157**, 127–138.

21 D. Bates and A. Eastman, *Br. J. Clin. Pharmacol.*, 2017, **83**, 255–268.
22 J. T. Ndongo, J. N. Mbing, M. F. Tala, A. Monteillier, D. E. Pegnyemb, M. Cuendet and H. Laatsch, *Phytochemistry*, 2017, **144**, 189–196.
23 K.-H. Lim, O. Hiraku, K. Komiyama and T.-S. Kam, *J. Nat. Prod.*, 2008, **71**, 1591–1594.
24 Y. Wang, F. Xie, B. Lin, M. Cheng and Y. Liu, *Chem. – Eur. J.*, 2018, **24**, 14302–14315.
25 S. Zeeli, T. Weill, E. Finkin-Groner, C. Bejar, M. Melamed, S. Furman, M. Zhenin, A. Nudelman and M. Weinstock, *J. Med. Chem.*, 2018, **61**, 4004–4019.
26 J. E. Wilson, R. Kurukulasuriya, M. Reibarkh, M. Reiter, A. Zwicker, K. Zhao, F. Zhang, R. Anand, V. J. Colandrea, A.-M. Cumiskey, A. Crespo, R. A. Duffy, B. Ann Murphy, K. Mitra, D. G. Johns, J. L. Duffy and P. Vachal, *ACS Med. Chem. Lett.*, 2016, **7**, 261–265.
27 F. De Moliner, L. Banfi, R. Riva and A. Basso, *Comb. Chem. High Throughput Screening*, 2011, **14**, 782–810.
28 D. Mondal, P. L. Kalar, S. Kori, S. Gayen and K. Das, *Curr. Org. Chem.*, 2020, **24**, 2665–2693.
29 G. W. Gribble, *Indole Ring Synthesis: From Natural Products to Drugs Discovery*, Wiley-VCH, Chichester, UK, 2016.
30 G. K. Hughes and F. Lions, *J. Proc. R. Soc. N. S. W.*, 1938, **71**, 494–502.
31 B. Witkop and J. B. Patrick, *J. Am. Chem. Soc.*, 1951, **73**, 1558–1564.
32 G. Jones and T. S. Stevens, *J. Chem. Soc.*, 1953, 2344–2350.
33 M. J. James, P. O'Brien, R. J. K. Taylor and W. P. Unsworth, *Chem. – Eur. J.*, 2016, **22**, 2856–2881.
34 K. G. Liu, A. J. Robichaud, J. R. Lo, J. F. Mattes and Y. Cai, *Org. Lett.*, 2006, **8**, 5769–5771.
35 Y.-K. Lim and C.-G. Cho, *Tetrahedron Lett.*, 2004, **45**, 1857–1859.
36 E. Yasui, M. Wada and N. Takamura, *Tetrahedron Lett.*, 2006, **47**, 743–746.
37 A. Guy, J.-P. Guetté and G. Lang, *Synthesis*, 1980, 222–223.
38 Y. Murakami, Y. Yokoyama, T. Miura, H. Hirasawa, Y. Kamimura and M. Izaki, *Heterocycles*, 1984, **22**, 1211–1216.
39 S. Gore, S. Baskaran and B. König, *Org. Lett.*, 2012, **14**, 4568–4571.
40 J. L. Rutherford, M. P. Rainka and S. L. Buchwald, *J. Am. Chem. Soc.*, 2002, **124**, 15168–15169.
41 H. R. Snyder and C. W. Smith, *J. Am. Chem. Soc.*, 2002, **65**, 2452–2454.
42 G. L. Rebeiro and B. M. Khadilkar, *Synthesis*, 2001, 370–372.
43 B. J. Stokes, H. Dong, B. E. Leslie, A. L. Pumphrey and T. G. Driver, *J. Am. Chem. Soc.*, 2007, **129**, 7500–7501.
44 B. Liu, C. Song, C. Sun, S. Zhou and J. Zhu, *J. Am. Chem. Soc.*, 2013, **135**, 16625–16631.
45 Y.-L. Li, J. Li, A.-L. Ma, Y.-N. Huang and J. Deng, *J. Org. Chem.*, 2015, **80**, 3841–3851.
46 S.-L. Cui, J. Wang and Y.-G. Wang, *J. Am. Chem. Soc.*, 2008, **130**, 13526–13527.
47 N. Zeidan, S. Bognar, S. Lee and M. Lautens, *Org. Lett.*, 2017, **19**, 5058–5061.
48 M. Sayyad, Y. Nanaji and M. K. Ghorai, *J. Org. Chem.*, 2015, **80**, 12659–12667.
49 D. Bhattacharya, D. W. Gammon and E. van Steen, *Catal. Lett.*, 1999, **61**, 93–97.
50 S. B. Mhaske and N. P. Argade, *Tetrahedron*, 2004, **60**, 3417–3420.
51 A. Dhakshinamoorthy and K. Pitchumani, *Appl. Catal., A*, 2005, **292**, 305–311.
52 R. A. Duval and J. R. Lever, *Green Chem.*, 2010, **12**, 304–309.
53 D. Q. Xu, J. Wu, S. P. Luo, J. X. Zhang, J. Y. Wu, X. H. Du and Z. Y. Xu, *Green Chem.*, 2009, **11**, 1239–1246.
54 S. P. M. Ventura, A. M. M. Gonçalves, T. Sintra, J. L. Pereira, F. Gonçalves and J. A. P. Coutinho, *Ecotoxicology*, 2013, **22**, 1–12.
55 T. P. Thuy Pham, C.-W. Cho and Y.-S. Yun, *Water Res.*, 2010, **44**, 352–372.
56 K. J. Ardila-Fierro and J. G. Hernández, *ChemSusChem*, 2021, **14**, 2145–2162.
57 S. Mateti, M. Mathesh, Z. Liu, T. Tao, T. Ramireddy, A. M. Glushenkov, W. Yang and Y. I. Chen, *Chem. Commun.*, 2021, **57**, 1080–1092.
58 E. Colacino, V. Isoni, D. Crawford and F. García, *Trends Chem.*, 2021, **3**, 335–339.
59 F. Puccetti, S. Lukin, K. Užarević, E. Colacino, I. Halasz, C. Bolm and J. G. Hernández, *Chem. – Eur. J.*, 2022, **28**, e202104409.
60 J. Andersen and J. Mack, *Green Chem.*, 2018, **20**, 1435–1443.
61 A. Porcheddu, E. Colacino, L. De Luca and F. Delogu, *ACS Catal.*, 2020, **10**, 8344–8394.
62 M. Pérez-Venegas and E. Juaristi, *ACS Sustainable Chem. Eng.*, 2020, **8**, 8881–8893.
63 J. L. Howard, Q. Cao and D. L. Browne, *Chem. Sci.*, 2018, **9**, 3080–3094.
64 J. G. Hernández and C. Bolm, *J. Org. Chem.*, 2017, **82**, 4007–4019.
65 E. Colacino, A. Porcheddu, C. Charnay and F. Delogu, *React. Chem. Eng.*, 2019, **4**, 1179–1188.
66 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 and D. C. Waddell, *Chem. Soc. Rev.*, 2012, **41**, 413–447.
67 W. Pickhardt, S. Grätz and L. Borchardt, *Chem. – Eur. J.*, 2020, **26**, 12903–12911.
68 T. Friščić, C. Mottillo and H. M. Titi, *Angew. Chem., Int. Ed.*, 2020, **59**, 1018–1029.
69 D. Virieux, F. Delogu, A. Porcheddu, F. García and E. Colacino, *J. Org. Chem.*, 2021, **86**, 13885–13894.
70 O. Galant, G. Cerfeda, A. S. McCalmont, S. L. James, A. Porcheddu, F. Delogu, D. E. Crawford, E. Colacino and S. Spatari, *ACS Sustainable Chem. Eng.*, 2022, **10**(4), 1430–1439.
71 Y. Qiu, K. Te Puni, C. C. Duplan, A. C. Lindsay and J. Sperry, *Tetrahedron Lett.*, 2021, **72**, 153068.

72 F. Krauskopf, K.-N. Truong, K. Rissanen and C. Bolm, *Org. Lett.*, 2021, **23**, 2699–2703.
73 For some examples on hydrazones synthesis by mechanochemistry, in batch and in continuous, please refer to: (*a*) E. Colacino, A. Porcheddu, I. Halasz, C. Charnay, F. Delogu, R. Guerra and J. Fullenwarth, *Green Chem.*, 2018, **20**, 12230–12238; (*b*) D. E. Crawford, A. Porcheddu, A. S. McCalmont, F. Delogu, S. L. James and E. Colacino, *ACS Sustainable Chem. Eng.*, 2020, **8**, 12230–12238.
74 For other mechanochemical rearrangements please refer to ref. 59 and 69.
75 G. W. Breton, *J. Org. Chem.*, 1997, **62**, 8952–8954.
76 T. Nishiguchi, K. Kawamine and T. Ohtsuka, *J. Org. Chem.*, 1992, **57**, 312–316.
77 K. K. Kapoor, B. A. Ganai, S. Kumar and C. S. Andotra, *Synth. Commun.*, 2006, **36**, 2727–2735.
78 R. Mocci, E. Colacino, L. De Luca, C. Fattuoni, A. Porcheddu and F. Delogu, *ACS Sustainable Chem. Eng.*, 2021, **9**, 2100–2114.
79 D. L. Hughes, *Org. Prep. Proced. Int.*, 1993, **25**, 607–632.
80 B. Robinson, *Chem. Rev.*, 1963, **63**, 373–401.
81 K. V. Butler, J. Kalin, C. Brochier, G. Vistoli, B. Langley and A. P. Kozikowski, *J. Am. Chem. Soc.*, 2010, **132**, 10842–10846.
82 A. I. Alfano, A. Zampella, E. Novellino, M. Brindisi and H. Lange, *React. Chem. Eng.*, 2020, **5**, 2091–2100.
83 A. I. Alfano, M. Brindisi and H. Lange, *Green Chem.*, 2021, **23**, 2233–2292.
84 Q.-F. Wu, C. Zheng and S.-L. You, *Angew. Chem., Int. Ed.*, 2012, **51**, 1680–1683.
85 K. G. Liu, J. R. Lo and A. J. Robichaud, *Tetrahedron*, 2010, **66**, 573–577.
86 B. G. Fiss, A. J. Richard, T. Friščić and A. Moores, *Can. J. Chem.*, 2021, **99**, 93–112.
87 T. Portada, D. Margetić and V. Štrukil, *Molecules*, 2018, **23**, 3163.
88 R. A. Sheldon, in *Organic synthesis; past, present and future*, Chem. Ind., 1992, pp. 903–906.
89 R. A. Sheldon, *Green Chem.*, 2017, **19**, 18–43.
90 R. A. Sheldon, *ACS Sustainable Chem. Eng.*, 2018, **6**, 32–48.
91 K. Van Aken, L. Strekowski and L. Patiny, *Beilstein J. Org. Chem.*, 2006, **2**(3), DOI: **10.1186/1860-5397-2-3**.
92 For more information on COST Action CA18112 'Mechanochemistry for Sustainable Industry': **https://www.mechsustind.eu/** (accessed Febrauary 18, 2022).
93 M. Baláž, L. Vella-Zarb, J. Hernandez, I. Halasz, D. E. Crawford, M. Krupička, V. André, A. Niidu, F. Garcia, L. Maini and E. Colacino, *Chem. Today*, 2019, **37**, 32–34.
94 J. G. Hernández, I. Halasz, D. E. Crawford, M. Krupicka, M. Baláž, V. André, L. Vella-Zarb, A. Niidu, F. García, L. Maini and E. Colacino, *Eur. J. Org. Chem.*, 2020, 8–9.
95 For more information: **https://www.cost.eu/** (accessed Febrauary 18, 2022).