ACS Sustainable Chemistry & Engineering

pubs.acs.org/journal/ascecg

Research Article

Mechanochemistry Applied to the Synthesis of X-ray Contrast Agent

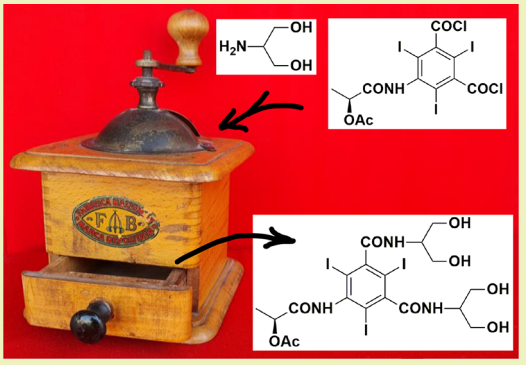
Alessandro Barge, Francesca Baricco, Giancarlo Cravotto,* Roberta Fretta, and Luciano Lattuada*

Cite This: *ACS Sustainable Chem. Eng.* 2020, 8, 12825−12830

Read Online

ACCESS | Metrics & More | Article Recommendations

ABSTRACT: Mechanochemical activation in planetary ball mills generates energy that is effective for the efficient, solvent-free syntheses of several types of organic molecules, including active pharmaceutical ingredients and diagnostic agents. X-ray-based procedures are the most commonly used of all diagnostic imaging techniques, because they offer several advantages, such as deep penetration, high resolution, and low cost. Iodinated X-ray contrast agents have long been used in medicine to facilitate and improve the acquisition of images by radiographic modalities. Iopamidol was the first agent developed in the field of nonionic X-ray contrast agents for imaging diagnosis and is still one of the most frequently used worldwide. We herein report an experimental investigation aimed to design a mechanochemical synthesis of Iopamidol, with the double goals of process intensification and either the elimination or significant reduction of the use of the high-boiling-point and reprotoxic solvent *N,N*-dimethylacetamide. The greener wet milling protocol gave Iopamidol in higher yields using safer solvents such as acetonitrile and *N,N*-dimethyloctanamide.

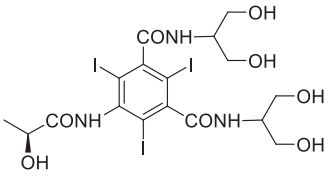


KEYWORDS: *Mechanochemistry, X-ray contrast agents, Iopamidol, Solvent-free, Green synthesis, Sustainable chemistry*

INTRODUCTION

X-ray imaging techniques have been widely utilized in diagnostic medicine since the discovery of X-rays by Wilhelm Roentgen in 1895, as they enable the noninvasive visualization of the human body's internal structure.[1−3] These diagnostic imaging modalities, such as, for example, angiography, urography, and computed tomography, are usually associated with the injection of an exogenous compound, called a contrast agent, which improves the quality of the images collected.[4−9] The most successful X-ray contrast agents in use are nonionic, water-soluble aromatic molecules that contain three iodine atoms. The success of these nonionic iodinated contrast agents, which have been on the market for more than 40 years, relies on their high tolerability, very low toxicity, and fast and complete elimination via the kidneys.[10,11] The great impact that these compounds have had on the world of medicine is worthy of note. In fact, more than 80 million doses are administered annually worldwide thanks to the production of several thousands of tons per year globally.[6,10,12]

Iopamidol **1** (Figure 1), patented in 1974,[13] was the pioneer molecule in the field of nonionic iodinated contrast agents, and it still sees widespread use the world over.[14−16] It is manufactured on a commodity scale via well-established organic reactions, including electrophilic aromatic iodination, N-acylation, and amidation.[17] In an attempt to continuously improve Iopamidol synthesis, we have previously explored the potential of emerging technologies to increase yields, reduce waste, and replace toxic reagents and solvents.[18−20] The past decade has witnessed the development of highly efficient alternative synthetic methods that make use of new enabling technologies. After preliminary tests, we found that mechanochemical methods have great potential to render these processes greener and more sustainable.



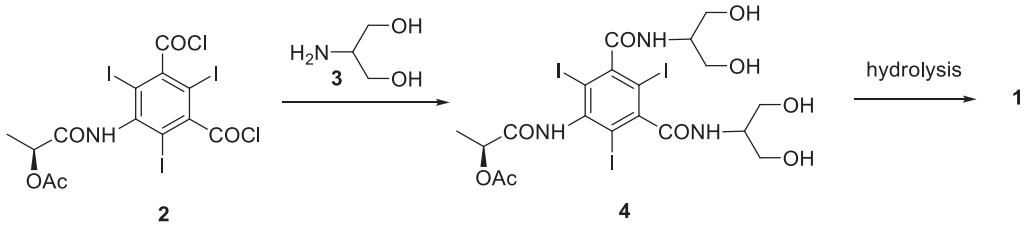
1

Figure 1. Iopamidol structure.

Mechanochemistry, or ball-milling, is a consolidated green technology that induces a chemical reaction by the direct absorption of mechanical energy.[21,22] This technique has found widespread applications in many scientific areas, such as inorganic chemistry, pharmaceutical cocrystals, catalysis, metal organic frameworks, as well as green and supramolecular

Received: April 19, 2020
Revised: July 3, 2020
Published: August 17, 2020

Scheme 1. Synthesis of Iopamidol



chemistry, just to name a few.[23] Mechanochemistry has, in particular, emerged as a valuable tool for organic synthesis.[24−27] One intriguing feature of mechanochemistry is the possibility to perform reactions without a solvent, and this, from an industrial point of view, is of paramount importance, as it may lead to the elimination of bulk volumes of costly, high boiling, and toxic solvents.[28] Metal leaching from mill surfaces and subsequent product contamination is often a drawback of ball milling, particularly when procedures are performed in high-speed planetary reactors with stainless steel jars and balls. Recent advances in ball-mill setups, with multisample jars, allow parallel syntheses to be performed for the preliminary screening of substrates, catalysts, and conditions on the milligram scale, before then moving to multigram and even multikilo scales for a semi-industrial production in a lab space.[29] Planetary ball mills are available on lab and pilot scales, which means with jar sizes of up to 5 L, and they are principally utilized to prepare valuable materials. Reactions performed with this technique are faster and cleaner than those performed under conventional methods and also furnish reagent, solvent, and energy savings.[30] Effective mixing with high stress frequencies is advantageous in chemical synthesis and can be achieved by the use of small balls at a constant filling ratio. Where reaction kinetics are slow, higher stress energies can be provided by large ball diameters, high ball densities, and a higher revolution speed. The counter-direction of rotational to revolution speed is more effective in refinement than the motion in a normal direction.[31]

In the final step of the Iopamidol synthesis, acyl chloride **2** is reacted with a slight excess of 2-amino-1,3-propandiol (serinol)[32] **3** in an aprotic dipolar solvent, which is needed to solubilize both the lipophilic intermediate **2** and the hydrophilic serinol **3** (Scheme 1). The solvent of choice for this reaction is *N,N*-dimethylacetamide (DMAc), because it gives cleaner reactions (a lower impurity profile) than dimethylformamide (DMF) and has a lower boiling point than *N*-methylpyrrolidone (NMP), making recovery easier. There has recently been increased concern about the use of DMAc, especially when used in bulk volumes, because of its reprotoxicity.[33−35] As no viable alternative solvents are currently available, a mechanochemical route has been selected, from among all the enabling technologies that are used in solvent-free protocols,[36] as a versatile strategy for the development of a synthetic protocol on lab to pilot scales.[37] While mechanochemical routes show particular versatility in organic syntheses, several authors have also highlighted how the ease of scalability and straightforward workup procedures can lead to environmentally friendly and cost-effective protocols.[38−40]

RESULTS AND DISCUSSION

The present work investigates a new process in which the amidation reaction, between acyl chloride **2** and an excess of serinol **3**, is performed under mechanochemical conditions that are either solvent-free or involve very low amounts, where the solvent acts as a humectant in a sort of wet milling. Table 1 summarizes the first part of the study, which aims to evaluate the impact of the critical parameters on reaction yield, namely, (i) the equivalents of serinol, (ii) the rotation speed, and (iii) the reaction time. After 20 min of milling at 400 rpm, the best excess of serinol was found to be over 4 equiv, and it was possible to improve the yield, up to 61%, after 70 min (entry 10). The yield could be increased even further at higher speed (650 rpm) and reached 81.8% in only 20 min (entry 18) and 89.4% after 40 min milling (entry 15).

Table 1. Parameter Optimization upon the Modification of One Variable

	reaction conditions[a]			
entry	serinol/acyl chloride (2) (ratio mol/mol)	rpm	time (min)	yield (%)
1	2			21.6
2	3			43.9
3	4	400	20	47.5
4	5			47.4
5	7			47.9
6			10	42.7
4			20	47.3
7			30	50.8
8	5	400	40	51.3
9			55	58.2
10			70	61.0
11			90	59.0
12			10	72.2
13			20	81.0
14			30	80.9
15	5	650	40	89.4
16			55	81.1
17		200		27.6
4	5	400	20	47.3
18[b]		650		81.8

[a]The reported yields have been determined by HPLC and are the average of triplicate experiments. [b]Repetition of entry 13.

The yield increased with time up to a plateau value (entries 6−11 and 12−16, Table 1), after which degradation decreased the yield. The degradation of the halogenated compounds under prolonged milling has been already reported.[41,42] The mechanical force at higher speed may transform the mixture into a sticky paste that hampered the correct motion of the milling balls and stopped the reaction. In both lab and pilot scales, a small amount of solvent, which acts as a lubricant, was

https://dx.doi.org/10.1021/acssuschemeng.0c02928
ACS Sustainable Chem. Eng. 2020, 8, 12825−12830

useful in reducing this phenomenon and further increasing the yield.

For the sake of comparison, it must be pointed out that, when the reaction was performed in the same conditions in a glass reactor equipped with a classical mechanical stirrer, the yield was negligible (less than 10% vs 47.4% of entry 4, as an example). This because the sticky reaction mixture remained spread on the reactor walls without effective agitation.

As the main goal of this investigation is the elimination, or substantial reduction, of the amount of DMAc, a wide screening of alternative solvents was performed under fixed conditions, as reported in Table 2. Surprisingly, three solvents behaved better than DMAc, namely, acetonitrile, diglyme, and *N,N*-dimethyloctanamide (entries 19−21).

Table 2. Solvent Screening under Selected Conditions[a]

entry	solvent	yield (%)
19	acetonitrile	83.7
20	diglyme	80.8
21	*N,N*-dimethyloctanamide	80.2
22	DMAc	79.5
23	diethylene glycol diethyl ether	78.7
24	1,4-dioxane	76.2
25	DMSO	76.1
26	*N,N*-dimethydecanamide	73.4
27	NMP	70.3
28	solventless	61.0
29	iso-dodecane	59.7
30	heptane	54.5
31	MEK	53.7
32	MPK	52.8
33	glycerine	50.3
34	*t*-butylacetate	46.8
35	water	1.0

[a]General conditions: Serinol/acyl chloride (**2**) = 5 (ratio mol/mol); rotation speed 400 rpm; time 70 min, acyl chloride (**2**)/solvent = 1:1 (g/mL).

A number of solvents (entries 19−27) enhanced the reaction outcome and increased yields. They probably exerted a dual role; lubricant and polar solvent. However, the reaction proceeded with a large excess of serinol (5 equiv, when the stoichiometry only requires 2), because it also acts as a proton scavenger. In view of the known positive effect of an additional base on the reaction outcome and the reduction of the serinol excess, a screening of common inorganic and organic bases was performed. The results obtained corroborate our hypothesis and indicated that Na_2CO_3 is the base of choice (Table 3). This allowed the excess of serinol to be reduced to 3 equiv (entry 42). Afterward, it was observed that a slight increase in milling time at 650 rpm increased the yield to 73.1% (Table 4, entry 45). Comparable results were achieved without the base and in an even shorter time by increasing the excess of serinol to 5 equiv (entry 47), although the economic impact on the process is much lower when using Na_2CO_3.

These findings prompted us to thoroughly investigate the possibility of using two common liquid organic bases, triethanolamine (TEOA) and *N*-methylmorpholine (NMM), for the double task of reducing the serinol excess and providing the effect of a glidant in the absence of a solvent (Table 5). A yield of ∼80% was achieved after 1 h of milling with TEOA, NMM, and a moderate excess of serinol (2.5−4 mol/mol).

Table 3. Solvent-Free Base Screening under Selected Conditions[a]

entry	base	serinol/acyl chloride (2) (ratio mol/mol)	yield (%)
1		2	21.6
36	Na_2CO_3	2	47.2
37	triethanolamine	2	35.9
38	CaO	2	16.0
39	triethylamine	2	23.2
40	NaOH	2	3.8
41	$CaCO_3$	2	1.5
42	Na_2CO_3	3	54.7
43	Na_2CO_3	4	55.5
44	Na_2CO_3	5	46.1

[a]General conditions: base amount/acyl chloride (**2**) = 5 (mol/mol); rotation speed 400 rpm; time 20 min.

Table 4. Na_2CO_3 (5 equiv) under Different Conditions

entry	base	serinol/acyl chloride (2) (ratio mol/mol)	rpm	time (min)	yield (%)
1	no base	2	400	20	21.6
36	Na_2CO_3	2	400	20	47.2
45	Na_2CO_3	2	650	30	73.1
46	Na_2CO_3	4	650	50	64.1
47	no base	5	650	10	72.2

Table 5. TEOA and NMM[a] Versus No Base[b]

entry	base	serinol/acyl chloride (2) (ratio mol/mol)	time (min)	yield (%)
48	no base	2	30	15.8
49	no base	2.5	30	16.2
50	TEOA	2	30	64.3
51	TEOA	2	60	61.8
52	TEOA	2.5	30	55.6
53	TEOA	2.5	60	78.5
54	TEOA	3	60	79.6
55	TEOA	4	60	80.0
56	TEOA	5	60	80.8
57	NMM	2.5	30	61.0
58	NMM	2.5	60	82.7
59	NMM	5	30	98.0

[a]The ratio of base/acyl chloride (**2**) = 5 mol/mol. [b]Milling at 650 rpm.

The experiments described herein indicate that the mechanochemical approach can be used as an effective alternative method for the preparation of Iopamidol. The addition of a small amount of solvent or, better, a small amount of a liquid base (TEOA), improved the reaction yield and also reduced the excess of serinol, making the process easier as well as more eco-friendly and cost-effective. On the basis of these considerations, the last part of this work focused on the scale-up of the reaction using a 5 L prototype, which is a double-jacket cooled drum equipped with hammers and balls, as depicted in Figure 2. This peculiar setup multiplies the number of collisions between the molecules of the reacting mixture and, thus, compensates for its much lower rotation speed, compared to a planetary mill. This reclining drum can easily be filled with the reacting mixture in a vertical position and then, at the end of the process, be fully emptied like a concrete mixer after the cover is unscrewed and removed. In

https://dx.doi.org/10.1021/acssuschemeng.0c02928
ACS Sustainable Chem. Eng. 2020, 8, 12825−12830

Figure 2. 5 L milling-drum prototype.

Figure 3 is visible the different aspect of the reacted mixture in solvent-free and wet milling conditions. The results were summarized in Table 6.

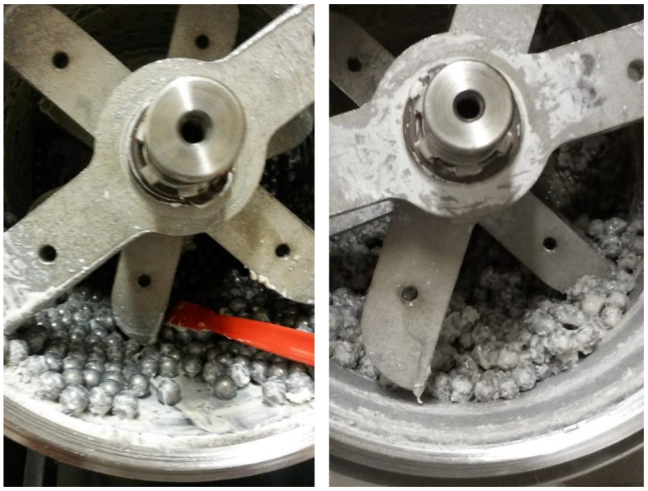


Figure 3. Reacted mixture in solvent-free (left) and wet milling (right) conditions (5 L milling drum).

CONCLUSIONS

In the search of greener and more efficient synthetic protocols for the most common X-ray contrast agent Iopamidol, we have investigated a mechanochemical protocol. Besides valuable process intensification, the amount of solvent employed has been reduced up to one-fifth compared to the industrial batch process, and this is a substantial reduction. Moreover, we were able to find a couple of safer solvents (acetonitrile and *N,N*-dimethyloctanamide), which gave higher yields than DMAc. The excellent results obtained on the lab scale with a planetary ball mill have been confirmed using a pilot-scale rotating drum, at the half-kilogram scale.

EXPERIMENTAL SECTION

A Retsch PM100 High Speed Planetary Ball Mill was used for all the lab-scale experiments. The stainless steel milling jar (50 mL) was charged with two types of stainless steel balls: Ø = 5 mm (50 balls) and Ø = 2 mm (1500 balls).

A 5 L ball mill prototype, designed by Mr. G. Omiccioli (Vibur Srl, Turin), was used for pilot-scale testing. The water-cooled double-jacket horizontal ball mill was charged with stainless steel balls with Ø = 15 mm (350 balls).

All commercially available reagents and solvents were used without further purification. Acyl chloride **2**, serinol **3**, acetyl Iopamidol **4**, and Iopamidol **1** were provided by Bracco Imaging Spa.

High-performance liquid chromatography (HPLC) analyses were performed on a Waters HPLC system (Waters 1525EF binary pump, Waters 717 plus autosampler, Waters 2996 diode array detector, Phenomenex Thermasphere TS130 column oven). The HPLC method used was the validated method reported for Iopamidol in European Pharmacopoeia,[43] which employs two Zorbax SB-Phenyl (80 Å 5 μm, 250 × 4.6 mm, Agilent Technologies) columns, connected in series, at an operative temperature of 60 °C. Elution was performed using water as solvent A and water/acetonitrile 1:1 as solvent B, with the following gradient profile: (min, B%) 0,0; 18,0; 40,38; 45,50; 50,0; 60,0. The UV detector was set at λ = 240 nm, and the flow rate was at 2 mL min^{-1}. The yield and purity of the acetyl Iopamidol recovered using the process was determined via the direct hydrolysis and HPLC analysis of the obtained product (Iopamidol), by comparison with the pure compound, which was used as an external standard (calibration curve with R^2 = 0.998).

Lab-Scale Iopamidol Synthesis (General Procedure). Solid acyl chloride (**2**) (1 g, 1.4 mmol), serinol (0.640 g; 7 mmol), and either an optional base (different amounts according to the experimental conditions chosen) or solvent (1 mL) were added to the jar. The jar was closed and inserted into the mill.

The milling process was performed at a range of revolutions per minute (rpm) values and reaction times. Once obtained, the crude acetyl Iopamidol **4** was not isolated but immediately converted to Iopamidol via hydrolysis. Hydrolysis procedure: after the crude reaction mixture was cooled to room temperature, 30% NaOH (~1 mL) was added directly to the jar, which was then subjected to 400 rpm for 10 min. The crude reaction was collected by washing the jar and balls with water (2 × 25 mL). The obtained solution was neutralized with 2 N HCl, and the yield and purity of the Iopamidol were determined in the crude by HPLC, using an external standard.

Pilot-Scale Iopamidol Synthesis (General Procedure). The stainless steel tank (5 L), equipped with five mechanical units with a double hammer fixed on the rotating axis (45° staggered), was charged with stainless steel balls with Ø = 15 mm (350 balls), solid acyl chloride **2** (300 g; 0.42 mol), and serinol **3** (192 g; 2.11 mol). Furthermore, in selected experiments, either DMAc or TEOA (300 mL) was added to the jar, which was maintained in a vertical position during loading. The tank was closed and placed obliquely in the mill to ensure that the balls had maximum mechanical efficiency inside the jar. The milling process was performed at a predetermined rotation frequency (40, 30, or 20 Hz) for 3 h. A tap water regular flow ensured the drum wall temperature was kept constant. The mixture was sampled at intermediate times by stopping the rotation and opening the reactor. Hydrolysis procedure: after the crude reaction mixture was cooled to room temperature, the jar and balls are washed with water, and the solution was recovered quantitatively. A 30% NaOH solution was then directly added to the collected solution to reach pH 10, and it was maintained under stirring overnight. Alternatively, the obtained aqueous solution of acetyl Iopamidol **4** was first eluted twice over a cationic ion-exchange resin (Dowex C350, Na^+ form), to fix the serinol and base in excess, then treated with 30% NaOH up to pH 10 and maintained under stirring for 7 h. The basic solution was then neutralized with 2 N HCl. The yield and purity of the isolated Iopamidol were determined by HPLC analysis of the crude solution, using an analytical sample of Iopamidol as an external standard.

https://dx.doi.org/10.1021/acssuschemeng.0c02928
ACS Sustainable Chem. Eng. 2020, 8, 12825−12830

Table 6. Reaction Scale-up[a]

entry	base	serinol/(2)(mol/mol)	solvent (mL)	acyl chloride (2) (g)	serinol (g)	rotationfreq (Hz)	time (h)	yield (%)
60	no	5/1	no	100	64.3	20	0.5	
							1	47.1
							2	49.3
							3	39.7
61	no	5/1	DMAc 300	300	192	40	0.5	76.2
							1	91.4
							2	76.2
							3	96.9
62	no	5/1	DMAc 150	300	192	30	0.5	79.6
							1	66.0
							2	83.5
							3	79.1
63	no	5/1	DMAc 500	500	320	10	0.5	82.0
							1	70.6
							2	83.8
							3	86.3
64	TEOA 93.5 mL	5/1	no	100	64.3	30	0.5	88.2
							1	86.6
							2	89.2
							3	86.4
65	TEOA 100 mL	2.5/1	no	100	32.4	30	0.5	85.1
							2	84.5
							3	67.2
							5	68.8

[a]Main parameters and conditions. Acyl chloride **2** (300 g; 0.42 mol), serinol **3** (192 g; 2.11 mol), either DMAc or TEOA (300 mL). The lower rotation frequency adopted in these larger-scale experiments is justified by the larger diameter of the drum and the double action of the hammers and balls, which guarantees the necessary mechanical energy to promote the reaction. The reaction reached the maximum yield after only 30−60 min under all of the explored conditions. Furthermore, the use of TEOA as solvent and base meant that it was possible to cut the amount of serinol used by half and only lose 3% of the yield (entries 64 and 65).

In one example (Entry 61; 3 h) the crude product was purified in order to assess the isolated yield of Iopamidol. The crude obtained after 3 h of milling was dissolved in water (1.9 L), and the solution was eluted on a cationic ion-exchange resin (Dowex C350, Na^+ form) to fix the serinol in excess, then treated with 30% NaOH up to pH 10 and maintained under stirring for 7 h. The basic solution was then neutralized with 2 N HCl. This solution was eluted on Amberlite XAD 1600 resin (1.5 L) with water until disappearance of the product. The eluate was concentrated to the volume of ∼1 L and eluted first on a cationic ion-exchange resin (Dowex C350, H^+ form, 3.5 L) and then on an anionic ion-exchange resin (Relite MG1, OH^- form, 3 L). The eluate was evaporated under vacuum, and the residue was crystallized with 2-butanol to obtain, after filtration and drying, 294 g (90% yield) of pure product (HPLC purity >99% in area%).

AUTHOR INFORMATION

Corresponding Authors

Giancarlo Cravotto − *Dipartimento di Scienza e Tecnologia del Farmaco and Centre for Nanostructured Interfaces and Surfaces, University of Turin, 10125 Turin, Italy;* orcid.org/0000-0001-7574-7350; Email: giancarlo.cravotto@unito.it

Luciano Lattuada − *Bracco Research Centre, Bracco Imaging SpA, 10010 Colleretto Giacosa, TO, Italy;* Email: luciano.lattuada@bracco.com

Authors

Alessandro Barge − *Dipartimento di Scienza e Tecnologia del Farmaco and Centre for Nanostructured Interfaces and Surfaces, University of Turin, 10125 Turin, Italy;* orcid.org/0000-0003-4638-6634

Francesca Baricco − *Dipartimento di Scienza e Tecnologia del Farmaco and Centre for Nanostructured Interfaces and Surfaces, University of Turin, 10125 Turin, Italy*

Roberta Fretta − *Bracco Research Centre, Bracco Imaging SpA, 10010 Colleretto Giacosa, TO, Italy*

Complete contact information is available at: https://pubs.acs.org/10.1021/acssuschemeng.0c02928

Author Contributions

The manuscript was written thanks to contributions of all the authors. All authors have given their approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This work was supported by Bracco Imaging SpA.

ABBREVIATIONS

Diglyme, diethylene glycol dimethyl ether; DMAc, *N,N*-dimethylacetamide; DMF, *N,N*-dimethylformamide,; DMSO, dimethyl sulfoxide; MEK, methyl ethyl ketone; MPK, methyl propyl ketone; NMM, *N*-methylmorpholine; NMP, *N*-methylpyrrolidone; TEOA, triethanolamine

REFERENCES

(1) Kalender, W. A. X-ray computed tomography. *Phys. Med. Biol.* **2006**, *51*, R29−R43.

(2) Linton, O. W. Medical Applications of X Rays. *Beam Line* **1995**, *2*, 25−34.

(3) Hendee, W. R. X-rays in medicine. *Phys. Today* **1995**, *48*, 51−56.
(4) Speck, U. *X-ray Contrast Media;* Springer: Berlin, Germany, 2018. DOI: 10.1007/978-3-662-56465-3.
(5) Frenzel, T.; Lawaczeck, R.; Taupitz, M.; Jost, G.; Lohrke, J.; Sieber, M. A.; Pietsch, H. Contrast Media for X-ray and Magnetic Resonance Imaging. *Invest. Radiol.* **2015**, *50*, 671−678.
(6) Lusic, H.; Grinstaff, M. W. X-ray-Computed Tomography Contrast Agents. *Chem. Rev.* **2013**, *113*, 1641−1666.
(7) Rutten, A.; Prokop, M. Contrast Agents in X-Ray Computed Tomography and Its Applications in Oncology. *Anti-Cancer Agents Med. Chem.* **2007**, *7*, 307−316.
(8) Krause, W.; Schneider, P. W. Chemistry of X-Ray Contrast Agents. *Top. Curr. Chem.* **2002**, *222*, 107−150.
(9) *Textbook of Contrast Media;* Dawson, P., Cosgrove, D. O., Grainger, R. G., Eds.; Martin Dunitz Ltd.: London, UK, 1999; pp 3−247. ISBN: 1899066314.
(10) Christiansen, C. X-ray contrast media − an overview. *Toxicology* **2005**, *209*, 185−187.
(11) McKinstry, D. N.; Rommel, A. J.; Sugerman, A. A. Pharmacokinetics, metabolism and excretion of iopamidol in healthy subjects. *Invest. Radiol.* **1984**, *19*, 171−174.
(12) Katzberg, R. W.; Haller, C. Contrast-induced nephrotoxicity: Clinical landscape. *Kidney Int.* **2006**, *69*, S3−S7.
(13) Felder, E.; Pitrè, D. E. Water-soluble, non-ionizing hydroxy-containing amide derivatives of 2,4,6-triiodo-isophthalic acid. U.S. Patent 4001323 1977; *Ger. Offen.* DE 2547789 1976.
(14) *The Merck Index,* 15th ed.; RSC Publishing, pp 940−941, 2013.
(15) Pitrè, D.; Felder, E. Development, Chemistry, and Physical Properties of Iopamidol and Its Analogues. *Invest. Radiol.* **1980**, *15*, S301−S309.
(16) Felder, E.; Grandi, M.; Pitrè, D.; Vittadini, G. In *Analytical Profiles of Drug Substances;* Florey, K., Ed.; Academic Press: San Diego, CA, 1988; Vol. *17*, pp 115−154.
(17) Anelli, P. L.; Brocchetta, M.; Lattuada, L.; Uggeri, F. Green approaches to the production of Iopamidol. *Pure Appl. Chem.* **2011**, *84*, 485−491.
(18) O'Brien, M.; Denton, R.; Ley, S. V. Lesser-Known Enabling Technologies for Organic Synthesis. *Synthesis* **2011**, *2011*, 1157−1192.
(19) Rubin, A. E.; Tummala, S.; Both, D. A.; Wang, C.; Delaney, E. J. Emerging Technologies Supporting Chemical Process R&D and Their Increasing Impact on Productivity in the Pharmaceutical Industry. *Chem. Rev.* **2006**, *106*, 2794−2810.
(20) *Green Techniques for Organic Synthesis and Medicinal Chemistry;* Zhang, W.; Cue, B. W., Jr., Eds.; John Wiley & Sons: Chichester, UK, 2012. ISBN: 978-1-119-28816-9l.
(21) James, S. L.; Adams, C. J.; Bolm, C.; Braga, D.; Collier, P.; Frïsčić, T.; Grepioni, F.; Harris, K. D. M.; Hyett, G.; Jones, W.; Krebs, A.; Mack, J.; Maini, L.; Orpen, A. G.; Parkin, I. P.; Shearouse, W. C.; Steed, J. W.; Waddell, D. C. Mechanochemistry: opportunities for new and cleaner synthesis. *Chem. Soc. Rev.* **2012**, *41*, 413−447.
(22) Stolle, A.; Szuppa, T.; Leonhardt, S. E. S.; Ondruschka, B. Ball milling in organic synthesis: solutions and challenges. *Chem. Soc. Rev.* **2011**, *40*, 2317−2329.
(23) James, S. L.; Frïsčić, T. Mechanochemistry. *Chem. Soc. Rev.* **2013**, *42*, 7494−7496.
(24) Howard, J. L.; Cao, Q.; Browne, D. L. Mechanochemistry as an emerging tool for molecular synthesis: what can it offer? *Chem. Sci.* **2018**, *9*, 3080−3094.
(25) Andersen, J.; Mack, J. Mechanochemistry and organic synthesis: from mystical to practical. *Green Chem.* **2018**, *20*, 1435−1443.
(26) Tan, D.; Frïsčić, T. Mechanochemistry for Organic Chemists: An Update. *Eur. J. Org. Chem.* **2018**, *2018*, 18−33.
(27) Wang, G.-W. Mechanochemical organic synthesis. *Chem. Soc. Rev.* **2013**, *42*, 7668−7700.
(28) Do, J.-L.; Frïsčić, T. Chemistry 2.0: Developing a New, Solvent-Free System of Chemical Synthesis Based on Mechanochemistry. *Synlett* **2017**, *28*, 2066−2092.
(29) Martina, K.; Rotolo, L.; Porcheddu, A.; Delogu, F.; Bysouth, S. R.; Cravotto, G.; Colacino, E. High Throughput Mechanochemistry: Application to Parallel Synthesis of Benzoxazines. *Chem. Commun.* **2018**, *54*, 551−554.
(30) Varma, R. S. Greener and Sustainable Trends in Synthesis of Organics and Nanomaterials. *ACS Sustainable Chem. Eng.* **2016**, *4*, 5866−5878.
(31) Burmeister, C. F.; Kwade, A. Process engineering with planetary ball mills. *Chem. Soc. Rev.* **2013**, *42*, 7660−7667.
(32) Andreessen, B.; Steinbüchel, A. Serinol: small molecule − big impact. *AMB Express* **2011**, *1*, 12.
(33) Byrne, F. P.; Jin, S.; Paggiola, G.; Petchey, T. H. M.; Clark, J. H.; Farmer, T. J.; Hunt, A. J.; McElroy, C. R.; Sherwood, J. Tools and techniques for solvent selection: green solvent selection guides. *Sustainable Chem. Processes* **2016**, *4*, 7.
(34) Ghazali, A. R.; Inayat-Hussain, S. H. *N,N-Dimethylacetamide in Encyclopedia of Toxicology,* 3rd ed.;Elsevier, 2014; pp 594−597. ISBN: 978-0-12-386454-3.
(35) Kennedy, G. L. Toxicology of dimethyl and monomethyl derivatives of acetamide and formamide: a second update. *Crit. Rev. Toxicol.* **2012**, *42*, 793−826.
(36) Cintas, P.; Tabasso, S.; Veselov, V. V.; Cravotto, G. Alternative reaction conditions: enabling technologies in solvent-free protocols. *Curr. Opinion Green Sust. Chem.* **2020**, *21*, 44−49.
(37) Cravotto, G.; Garella, D.; Carnaroglio, D.; Calcio Gaudino, E.; Rosati, O. Solvent-free chemoselective oxidation of thioethers and thiophenes by mechanical milling. *Chem. Commun.* **2012**, *48*, 11632−11634.
(38) Aakeröy, C. B.; Sinha, A. S.; Epa, K. N.; Spartz, C. L.; Desper, J. A versatile and green mechanochemical route for aldehyde−oxime conversions. *Chem. Commun.* **2012**, *48*, 11289−11291.
(39) Martina, K.; Baricco, F.; Berlier, G.; Caporaso, M.; Cravotto, G. Efficient green protocols for the preparation of highly functionalized *β*-cyclodextrin grafted silica. *ACS Sustainable Chem. Eng.* **2014**, *2*, 2595−2603.
(40) Jicsinszky, L.; Caporaso, M.; Tuza, K.; Martina, K.; Calcio Gaudino, E.; Cravotto, G. Nucleophilic substitutions of 6^{I}-O-monotosyl-*β*-cyclodextrin in planetary ball mill. *ACS Sustainable Chem. Eng.* **2016**, *4*, 919−929.
(41) Wang, R.; Zhu, Z.; Tan, S.; Guo, J.; Xu, Z. Mechanochemical degradation of brominated flame retardants in waste printed. *J. Hazard. Mater.* **2020**, *385*, 121509.
(42) Nomura, Y.; Nakai, S.; Hosomi, M. Elucidation of Degradation Mechanism of Dioxins during Mechanochemical Treatment. *Environ. Sci. Technol.* **2005**, *39*, 3799−3804.
(43) EDQM. *European Pharmacopoeia,* 10th ed.; Council of Europe: Strasbourg, France, 2019.