MEDICINAL MECHANOCHEMISTRY, AN EFFICIENT AND ENVIRONMENTALLY-FRIEND APPROACH FOR THE SYNTHESIS OF PZ-1190, A MULTI-TARGET SEROTONIN AND DOPAMINE RECEPTOR LIGAND WITH ANTIPSYCHOTIC PROPERTIES

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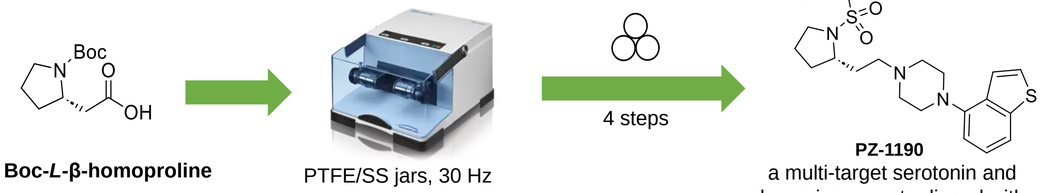
3rd Synthesis in Drug Discovery and Development

Introduction

In the last decade, mechanochemistry has been recognized as a powerful tool enabling efficient and sustainable organic syntheses [1,2]. Indeed, a growing number of mechanochemical procedures for generating active pharmaceutical ingredients (APIs) [3,4], and for a greener synthesis of biologically active compounds [5-7] have been reported so far and led to coining the term "*medicinal mechanochemistry*". Taking into account the benefits over classic in-batch procedure and extending the concept of medicinal mechanochemistry, we applied a solid-state approach for the synthesis of **PZ-1190**, a multi-target serotonin and dopamine receptor ligand with promising antipsychotic properties in rodents [8]. Herein, we present the development of an efficient and enviromentally-friendly protocol to overcome the limits related to in-solution synthesis of PZ-1190 [8] by the **improvement of overall isolated yield, the reduction of reaction time as well as limitation in the use of organic solvents and toxic reagents.**

Medicinal mechanochemistry approach



Boc-*L*-β-homoproline

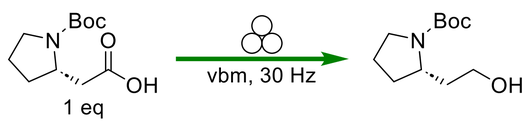
PTFE/SS jars, 30 Hz

a multi-target serotonin and dopamine receptor ligand with antipsychotic properties in rodents

Results

All the experiments were performed using a vibratory ball-mill – Retsch Mixer Mill MM 400, operated at 30 Hz and 10/35 mL stainless steel (SS) or PTFE jars equipped with one stainless steel ball (⌀=1.5 cm). All of the reactions were carried out under air and ambient temperature.

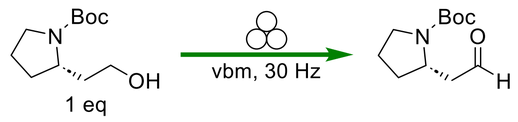
Reduction of carboxylic acid



Entry	Reducing agent	Activating agent	Volume of jars (mL)	Milling time (min.)	%Conv.[a]/Yield[b]
1	Sodium borohydride (1.5 eq)	Lithium chloride (4.5 eq)	10	150	50/-
2				360	60/-
		Methanesulfonyl chloride (1.2 eq)	10	25	67/-
4		1,1′-Carbonyldiimidazole CDI (1.2 eq)	10	20	97/-
5			35	**20**	**94/86**

Selected reaction conditions were presented: SS jars; total mass of reagents: 125 mg or 500 mg;. [a]Conversions were determined by HPLC analysis. [b]Yield was calculated atfer extraction with AcOEt (15 mL) and washing with 5% aqueous HCl solution (1 x 5 mL) and distilled water (1 x 5 mL). Results are means of two independent experiments.

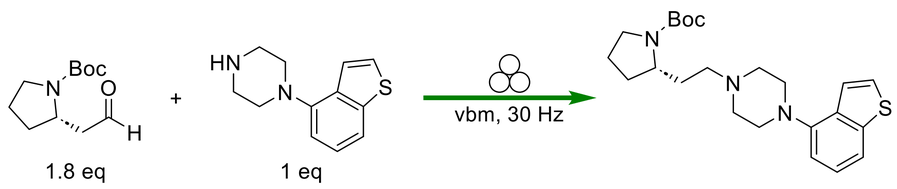
Oxidation of primary alcohol



Entry	Oxidizing agent	Volume of jars (mL)	Milling time (min.)	%Conv.[a]/Yield[b]
1	2-Iodoxybenzoic acid IBX (0.5 eq)	10	45	93/-
2	Dess–Martin periodinane DMP (0.5 eq)	10	30	100/-
3		35	**30**	**100/76**

Selected reaction conditions were presented: SS jars; total mass of reagents: 125 mg or 500 mg. [a]Conversion were determined by HPLC analysis. [b]Yield was calculated atfer extraction with AcOEt (15 mL) and washing with saturated solution of sodium thiosulfate (2 x 5 mL) and distilled water (2 x 5 mL). Results are means of two independent experiments.

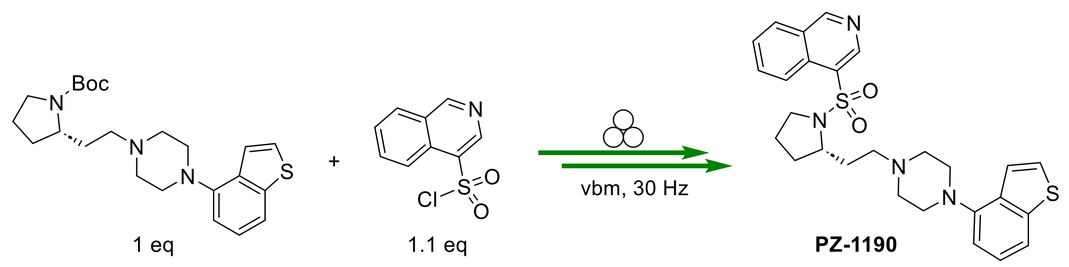
Reductive amination



Entry	Reducing agent	Volume of jars (mL)	Milling time (min.)	%Conv.[a]/Yield[b]
1	Sodium triacetoxyborohydride	10	135	71/-
2	Sodium cyanoborohydride	10	60	83/-
3			135	96/-
4		35	**135**	**99/91**

Selected reaction conditions are presented: SS jars; total mass of reagents: 125 mg or 500 mg; aldehyde and CH_3COOH (100 µL; η = 0.2) were introduced in jar in two equal portions, second portion was added after 1 h of milling. [a]Conversions were determined by HPLC analysis. [b]Yield was calculated atfer extraction with AcOEt (15 mL) and washing with saturated $NaHCO_3$ solution (2 x 5 mL), distilled water (2 x 5 mL), saturated NaCl solution (1 x 5 mL). Results are means of two independent experiments.

Deprotection and sulfonylation of secondary amine



Entry	Deprotection procedure	Base	Reaction time of two steps (min.)	%Conv.[c]/Yield[d]
1[a]	HCl_g	K_2CO_3 (1.2 eq)	125 (120 + 5)	100/82
2[b]	6M HCl in *i*-PrOH	K_2CO_3 (5 eq)	**35** (30 + 5)	**100/94**

Selected reaction conditions are presented: 35 mL SS or PTFE jars; [a]The reaction was carried out with secondary amine obtained after deprotection in solid state by using gaseous HCl; [b]The reaction was carried out with secondary amine obtained after deprotection by using 6M HCl in *i*-PrOH in ball mill (one pot two steps procedure); [c]Conversions were determined by HPLC analysis. [d]Yield was calculated after washing with distilled water (5 x 8 mL). Results are means of two independent experiments.

Conclusions

- An efficient and sustainable approach employing mechanochemistry methodology has been developed for the synthesis of PZ-1190, a potent multi-target ligand with antipsychotic activity in rodents, in a gram scale.
- To the best of our knowledge, performed reactions represent a rare example of mechanochemical reduction of a carboxylic function, oxidation of an aliphatic hydroxylic group into aldehyde as well as deprotection of Boc function group.
- Elaborated protocol allowed to avoid the use of environmentally unfriendly solvent such as **DCM, THF, hexane** as well the need of **column chromatography purification** for all intermediates and final compound, displaying better green chemistry metrics (EcoScale, E-factor).

In solution synthesis

- Avarage overall isolated yield: **38%**
- The use of environmentally unfriendly reagents and solvents: **DCM, THF, $LiAlH_4$, TFA**
- Prolonged: **42 h**
- Purification by **column chromatography**
- Low sustainable: **EcoScale** value per each reaction **< 50**; **E-factor = 6692.83**

Mechanochemical approach

- Good overall isolated yield: **56%**
- The use of solvents was limited
- Rapid: **< 4 h**
- All compounds were obtained by simply **extraction**
- Sustainable: **EcoScale** value per each reaction **> 70**; **E-factor = 623.34**

- The obtained results prove the suitability of mechanochemistry as a sustainable and efficient method for the multi-step synthesis of biologically active compounds and might facilitate the integration of the medicinal mechanochemistry as a key component of lead discovery programs in both academic and industrial research.

References

[1] Tan, D. *et al. Chem. Commun*. **2016**, *52*, 7760−7781.
[2] Ardila-Fierro, K.J. & Hernandez, J.G. *ChemSusChem.* **2021**, *14*, 2145–2162.
[3] Friščić, T. *et al. Angew. Chem.* **2020**, *59,* 1018−1029.
[4] Colacino, E. *et al. React. Chem. Eng.* **2019**, *4*, 1179−1188.
[5] Canale, V. *et al. J. Org. Chem.* **2020**, *85*, 10958−10965.
[6] Bento, O. *et al. Eur. J. Org. Chem.* **2022**, e202101516.
[7] Canale, V. *et al. Biomolecules*. **2023**, 13, 12.
[8] Zajdel, P. *et al. Eur. J. Med. Chem.* **2018**, *145*, 790–804.

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