Sustainable Chemistry and Pharmacy 5 (2017) 14–21

Contents lists available at ScienceDirect

Sustainable Chemistry and Pharmacy

journal homepage: www.elsevier.com/locate/scp

Ball mill and microwave assisted synthetic routes to Fluoxetine

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ARTICLE INFO

Keywords:
Mechanochemistry
Ball mill
Microwave
Fluoxetine
Antidepressant

ABSTRACT

Remarkable advances have been made in the development of an environmentally-friendly approach for the rapid and simple construction of the Active Pharmaceutical Ingredient (API) Fluoxetine (**1**). These include the use of ball milling and microwave irradiation as greener alternatives – compared to conventional heating – to provide the energy needed for the chemical transformations.

1. Introduction

Pharmaceutical manufacturing is the most solvent-intensive and the least efficient of all chemical industries in terms of waste generated per unit of product. Statistics compiled across the industry point to an average waste-to-product ratio of 200. In other words, factories generate 200 kg of waste for every kilogram of active pharmaceutical ingredient produced and the financial burden associated with the processing and disposal of these sizeable waste-streams is considerable (Rajagopal, 2014). Furthermore, pharmaceutical manufacturing plants devote exorbitant amounts of money each year for the fuel and electricity they need to keep their facilities running (Galitsky et al., 2008). As a counter to this, various "green" approaches have become popular as a means to reduce the ecological impact of the pharmaceutical industry including the use of solvent-free synthetic procedures and alternative energy sources (Markarian, 2016). In this context, mechanosynthesis [or synthesis in a ball mill (Tan et al., 2016)] and microwave assisted synthesis (Wagner, 2006; Sekhon, 2010), have recently become very popular as cleaner technologies in the pharmaceutical sector (Cernansky, 2015).

Mechanosynthetic methods – grinding of (solid) reactants in a ball mill – avoid the use of solvents and at the same time utilize mechanical energy from the grinding for the formation/ breaking of new bonds (André et al. 2011; Baig and Varma, 2012; Bonnamour et al., 2013; James et al., 2012, Jones and Eddleston, 2014, Konnert et al., 2014, 2016; Tan et al., 2014, 2016.). Similarly, microwave assisted synthesis is particularly interesting due to its high efficiency, leading to drastically reduced reaction times and higher yields, both of which result in energy savings. In addition, there is clear evidence that these technologies offer new opportunities to the synthetic chemist in the form of complementary reactions that are not possible using conventional methods. As such, both mechano- and microwave assisted synthesis provide a general answer to the demands of pharmaceutical industry for cleaner, safer and efficient synthetic solutions. Their implementation into the pharmaceutical industry could lead to a decrease in the number of process operations, thus allowing both the simplification of the processes and the reduction of costs to the manufacturer and, ultimately, to the consumer (Bruckmann et al., 2008; Mikhailenko et al., 2004).

This work focuses on the synthesis of the antidepressant Fluoxetine (commercialised as Prozac), via environmentally-friendly ball milling and microwave assisted techniques. A simplified and fast synthetic pathway for the eco-friendly synthesis of Fluoxetine is here reported, where the utilisation of solvent and energy consumption have been minimized.

2. Materials and methods

2.1. General instrumentation

2.1.1. TLC

Thin layer chromatography (TLC) was run on silica gel 60 aluminium sheets, 0.25 mm thick (F_{254}*Merck KGaA*®). The components were visualized by UV light (254 nm), phosphomolybdic acid or $KMnO_4$ staining solutions.

2.1.2. IR

IR spectra were recorded on *Nicolet*® 380 FT/IR – Fourier Transform Infrared Spectrometer. Only the most significant frequencies have been considered for the characterisation, and have been

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http://dx.doi.org/10.1016/j.scp.2016.11.003
Received 23 August 2016; Received in revised form 13 November 2016; Accepted 26 November 2016

reported in cm^{-1}.

2.1.3. NMR

^{1}H NMR, ^{13}C NMR and ^{19}F NMR were recorded on a *JEOL*® ECS-400 (400, 100.6 and 376.5 MHz, respectively) using $CDCl_3$ as solvent. Chemical shift values are reported in ppm with TMS as internal standard ($CDCl_3$: δ 7.26 for ^{1}H NMR, δ 77.0 for ^{13}C NMR). Data are reported as follows: chemical shifts, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad), coupling constants (Hz), and integration.

2.1.4. Flash chromatography

Column chromatography was carried out using *Geduran*® Silica gel 60, 40–63 μm RE.

2.1.5. Melting points

Melting points were measured in a *Stuart*® SMP10 melting point apparatus and are not corrected.

2.1.6. GCMS

Low resolution mass spectra were recorded on a GC-MS spectrometer (*Hewlett Packard*® HP 5890 Series II GC System) equipped with a DB-5 column (*J & W Scientific*®, 30 m×0.32 mm), connected to a *Hewlett Packard*® HP 5972 Series Mass Selective Detector. Helium was used as carrier gas at 10 psi, and the samples were ionized by an electronic impact (EI) source at 70 eV.

2.1.7. HRMS

High resolution mass spectra were obtained on a *Agilent Technologies*® 6540 Ultra-High-Definition (UHD) Accurate-Mass equipped with a time of flight (Q-TOF) analyzer and the samples were ionized by ESI techniques and introduced through a high pressure liquid chromatography (HPLC) model *Agilent Technologies*® 1260 Infinity Quaternary LC system. Samples were eluted with mixture of MeOH and 0.1% formic acid, with a flow of 0.2 mL/min.

2.1.8. Shaker ball mill

Reactions in the shaker ball mill were carried out in a *Retsch*® MM200 (shaker mill) using a 25 mL stainless steel grinding jar provided with one stainless steel grinding ball of 2.5 cm of diameter.

2.1.9. Planetary ball mill

Reactions in the planetary ball mill were carried out in a *Retsch*® PM100 using a 50 mL stainless steel grinding jar and different sets of the grinding balls: (a) 2 stainless steel grinding balls of 1.5 cm diameter each, (b) 5 stainless steel grinding balls of 1 cm diameter each, (c) 10 stainless steel grinding balls of 0.8 cm diameter each, (d) 10 stainless steel grinding balls of 0.7 cm diameter each, (e) 5 stainless steel grinding balls of 0.6 cm diameter each, (f) 10 stainless steel grinding balls of 0.4 cm diameter each, or (d) 20 zirconium-coated grinding balls of 0.3 cm diameter each.

2.1.10. MW

The microwave irradiation was carried out in an *Anton Paar*® Monowave 300, Microwave Synthesis Reactor, using 10 and 30 mL glass vials sealed with a PTFE-coated silicone septum and closed with a snap cap made of PEEK.

2.2. General methods and considerations

All commercially available reagents were purchased from Aldrich, Acros, Alfa Aesar and Maybridge and used without further purification, unless stated otherwise.

2.2.1. Ball mill reactions

Before starting the grinding process, the grinding jar was flushed for 0.5 min with a stream of argon after all the reagents were added.

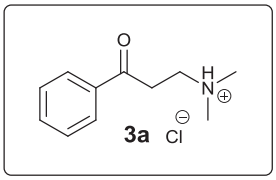
2.2.2. MW reactions

A dry MW-glass vial was filled with argon and sealed with a rubber septum. All the chemicals were added under argon atmosphere. The septum was quickly changed for a snap cap before putting the vial inside the Microwave Synthesis Reactor.

2.3. Experimental procedure and data of compounds

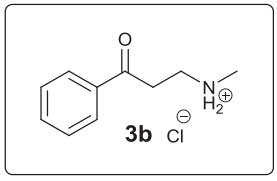
2.3.1. Mannich reactions

2.3.1.1. 3-(Dimethylamino)propiophenone hydrochloride (3a) (Istanbullu et al., 2015).



Concentrated HCl (40 μL, 0.5 mmol) was added dropwise to a solution of acetophenone (961 mg, 8 mmol), dimethylamine hydrochloride (832 mg, 10 mmol) and paraformaldehyde (360 mg, 12 mmol) in ^{i}PrOH (4 mL) at RT under Ar atmosphere, in a 30 mL MW glass tube. The mixture was heated in the MW to 110 °C for 60 min and a solid precipitated inside the glass tube. The resulting solid was filtrated and washed with acetone and concentrated under vacuum. Pure 3-(dimethylamino)propiophenone hydrochloride (**3a**) was obtained as a white solid (1.099 g, 65%). $\mathbf{M_p}$=153–156 °C [lit. M_p=153–154 °C (Roman et al., 2013)]. **IR** (ATR) 3400 (br), 2946, 2662, 1674, 1334, 1222, 958 $cm^{-1.}$ **^{1}H NMR** (400 MHz, CD_3OD) δ 8.80–7.20 (5H, m, ArH), 4.45–2.25 (4H, m, $CH_2CH_2N(CH_3)_2$), 3.75 (6H, s, $N(CH_3)_2$). **^{13}C NMR** (100.6 MHz, CD_3OD) δ 198.3, 137.2, 135.0, 129.9, 129.3, 54.4, 43.9, 34.2. Data in agreement with the literature.

2.3.1.2. 3-(Methylamino)-1-phenylpropan-1-one hydrochloride (3b) (Hu et al., 2015).



Concentrated HCl (125 μL, 1.5 mmol) was added dropwise to a solution of acetophenone (3.004 g, 25 mmol), methylamine hydrochloride (1.86 g, 27.5 mmol) and paraformaldehyde (1.05 g, 35 mmol) in EtOH (12.5 mL) at RT under Ar atmosphere, in a 30 mL MW glass tube. The mixture was heated in the MW to 130 °C for 5 h. The solvent was then concentrated under vacuum and the crude was purified by recrystallization (^{i}PrOH/AcOEt) to afford pure 3-(methylamino)-1-phenylpropan-1-one hydrochloride (**3b**) as a white solid (2.818 g, 57%). $\mathbf{M_p}$=113–118 °C [lit M_p=113–115 °C (Hu et al., 2015)]. **IR** (ATR) 3390 (br), 2941, 2694, 2448, 1679, 1373, 1223, 749 $cm^{-1.}$ **^{1}H NMR** (400 MHz, CD_3OD) δ 8.10–7.45 (5H, m, ArH), 3.58–3.35 (4H, m, $CH_2CH_2NCH_3$), 2.77 (3H, s, NCH_3). **^{13}C NMR** (100.6 MHz, CD_3OD) δ 198.6, 137.2, 135.0, 129.9, 129.3, 45.5, 35.5, 34.1. Data in agreement with the literature.

2.3.2. Carbonyl reduction in the shaker mill

2.3.2.1. 3-Dimethylamino-1-phenylpropan-1-ol (4a) (Xu and Langer, 2015).