Alternative Synthesis of Paracetamol and Aspirin under Non-conventional Conditions

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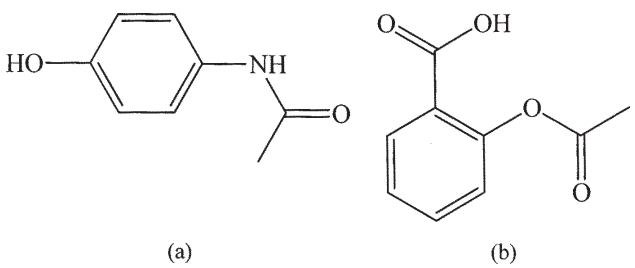
The paper deals with an alternative route for the synthesis of N-acetyl-p-aminophenol (paracetamol, PAR) and acetylsalicylic acid (aspirin, ASA) using principles of green chemistry, namely solvent-free synthesis combined with microwave-energy irradiation. The synthesis was carried out using salicylic acid and 4-aminophenol, acetic anhydride and no catalyst, under microwave irradiation. The yields were 92.4% for PAR and 81.6% for ASA. The compounds were identified by comparison with high-purity standards by the means of thin layer chromatography (TLC), melting point (m.p.) and FTIR spectroscopy.

Keywords: paracetamol, aspirin, microwave irradiation, green chemistry, synthesis

Over-the-counter drugs (known as OTCs) are pharmaceutical formulations that can be legally sold directly to a patient without a doctors' prescription, after proving that that formulation does not have an abuse potential, but possess a significant efficiency, tolerability and safety. OTC drugs are generally sold in order to treat minor health conditions that do not require the necessity of supervision of a physician. One of the oldest OTC drugs is acetylsalicylic acid (ASA), known as aspirin. Aspirin is a highly-used drug for the treatment of numerous conditions such as pain and aches [1], fever [2], rheumatic and inflammatory diseases, such as rheumatoid arthritis [3], pericarditis [4] and Kawasaki disease [5]. Recent studies are indicating that ASA is effective at preventing colorectal cancer [6] and prostate cancer [7]. Also, low doses of ASA reduce the risk of heart attack [8] and stroke [9].

Paracetamol (N-acetyl-p-aminophenol, PAR) is nowadays a widely used OTC drug in numerous countries and in different pharmaceutical formulations, alone or in combination with other active pharmaceutical ingredients. Drugs containing PAR are used in the treatment and/or relief of minor aches and pains [10] and is included in formulations for cold and flu remedies due to its antipyretic effect [11]. Paracetamol is used in the treatment and relief of severe pain such as post-operative pain [12] and providing palliative care in terminal stage cancer patients [13].

The chemical structures of paracetamol (PAR) and aspirin (ASA) are presented in figure 1.



(a) (b)

Fig. 1. Chemical structures of PAR (a) and ASA (b)

Demand for OTC drugs determined an increasing necessity for the synthesis of active pharmaceutical ingredients, and for ASA and PAR statistics shown that in the world over 145.000 tonnes per year of PAR were synthesized [14], while for ASA, over 40.000 tonnes are consumed each year [15]. These huge quantities required for pharmaceutical industry, corroborated with financial aspects regarding the economic efficiency, lead to the necessity of obtaining these compounds *via* alternative routes in order to achieve high purity in short periods of time and with the use of a minimum amount of solvent(s). Recent trends and strategies regarding organic synthesis are reunited under the name of "green chemistry", which is defined by IUPAC [16] as "the engineering concept of pollution prevention and zero waste both at laboratory and industrial scales. Green chemistry encourages the use of economical and ecocompatible techniques that not only improve the yield but also bring down the cost of disposal of wastes at the end of a chemical process".

Nowadays, microwave-assisted synthesis is widely used especially in the field of organic chemistry and in pharmaceutical industry for the oriented-synthesis of targeted compounds. Microwave irradiation is regarded as an alternative route for supplying energy to the reagents instead of using conventional methods, such as heating. The energy supplying is based on the interaction between electromagnetic radiation and molecules, namely the ability of mobile electric charges to transform electromagnetic energy into heat. Microwave-assisted reactions are considerable faster, cleaner, economic and eco-friendly comparative to classical organic synthesis [17].

According to this, we set our goal in the synthesis of paracetamol (PAR) and aspirin (ASA) *via* a green chemistry route consisting of a solvent-free reaction under microwave-energy irradiation.

Experimental part

Materials and methods

The reagents were commercial products: salicylic acid (Reactivul Bucureşti, purity > 99%), 4-aminophenol (Sigma-Aldrich, purity ≥ 99%) and acetic anhydride (Sigma-Aldrich,

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ReagentPlus®, purity ≥ 99%), and used as received, without further purification. Pure paracetamol and aspirin were obtained from Sigma-Aldrich and were used as standards. "Solvent free" chemical synthesis was carried out in a glass vial that was inserted in a sealed Teflon flask that was subject to microwave irradiation in an Elta domestic oven at 600W for an optimized time. All the experiments were carried out under the fume hood.

Melting points were determined on a Böetius PHMK (Veb Analytik Dresden) instrument, and thin-layer chromatography was carried out on silica gel-coated plates 60 F_{254} Merck using ethyl acetate as eluent. Chromatographic spots were revealed under UV light (λ=254 nm) followed by the subjection of the TLC plates in iodine vapours. IR spectra were recorded for a dispersion of the substance in KBr pellets (Specac Pellet Press) on a Jasco FT/IR-410 spectrophotometer, with a resolution of 1 cm^{-1} on 4000-600 cm^{-1} spectral range. Spectra were built up after a number of 16 acquisitions.

Microwave-induced synthesis of ASA

In a glass vial, 1.318 g (0.01 mol) of salicylic acid was treated with 1.4 mL (1.429g, 0.014 mol) of acetic anhydride. The vial was closed with a ground glass stopper having a 0.5 mm pierce (in order to avoid the pressure increasing in the vial during chemical reaction). The mixture was manually homogenised so a good contact between the solid and liquid phases occur. The vial was inserted in a Teflon flask and subject to microwave irradiation at 600W for 3 min. After irradiation stopped, the hot vial content was poured into a beaker containing 10 mL of cold water (5°C), placed in an ice bath, under magnetic stirring. After several minutes, a white crystalline solid separated. The suspension was filtered under reduced pressure while cold, washed with cold water (3x1 mL), and finally with 1 mL of n-propanol:water mixture 7:3 (v/v). The solid was then dried at 60 °C for 2h.

Acetylsalicylic acid

White crystals (1.47g, yield 81.6%) TLC one spot (R_f=0.46)

M.p. 135-136 °C

FTIR (KBr, cm^{-1}): 3392-2739(broad, peak 3022, 2883(shoulder), 2830(shoulder)), 1753, 1692, 1605, 1457, 1371, 1306, 1220, 1187, 1094, 1012, 916, 803, 754, 704

Microwave-induced synthesis of PAR

In a glass vial, 1.09 g (0.01 mol) of 4-aminophenol was suspended in 2 mL of distilled water, then treated with 1.0 mL (1.08g, 0.01 mol) of acetic anhydride. The vial was closed with a ground glass stopper having a 0.5 mm pierce, then inserted in a Teflon flask and subjected to microwave irradiation at 600W for 2 min. After irradiation stopped, the vial was cooled by insertion in an ice bath, and then filtered under reduced pressure. The remained solid was dried, and then recrystallized from the minimum amount of hot water. The recrystallized solid was then dried at 60°C for 2h.

N-acetyl-p-aminophenol

White crystals (1.47g, yield 92.4%), TLC one spot (R_f=0.24)

M.p. 169-170 °C

FTIR (KBr, cm^{-1}): 3323, 3161, 1650, 1610, 1561, 1505, 1439, 1372, 1327, 1259, 1225, 1172, 1108, 1015, 968, 836, 807, 796, 713, 685

Results and discussions

Synthesis of ASA and PAR

As previously stated, we set our goal in the synthesis of paracetamol (PAR) and aspirin (ASA) *via* a green chemistry route consisting of a solvent-free reaction under microwave-energy irradiation due to the fact that different results regarding these syntheses were previously published in literature, mentioning reaction times from 1 min. to 15 min. and yields from 65 to 92% [17-23].

The syntheses of both bioactive molecules (ASA and PAR) were carried out by the modification of syntheses mentioned in literature [23], according to figure 2.

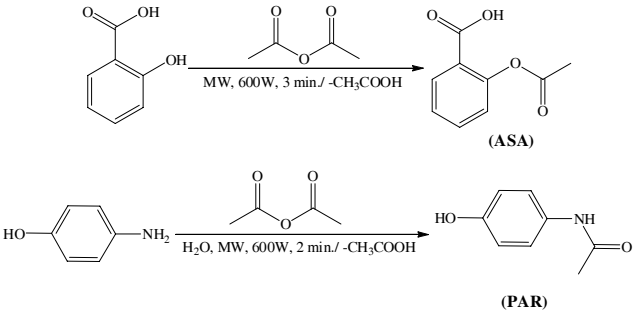
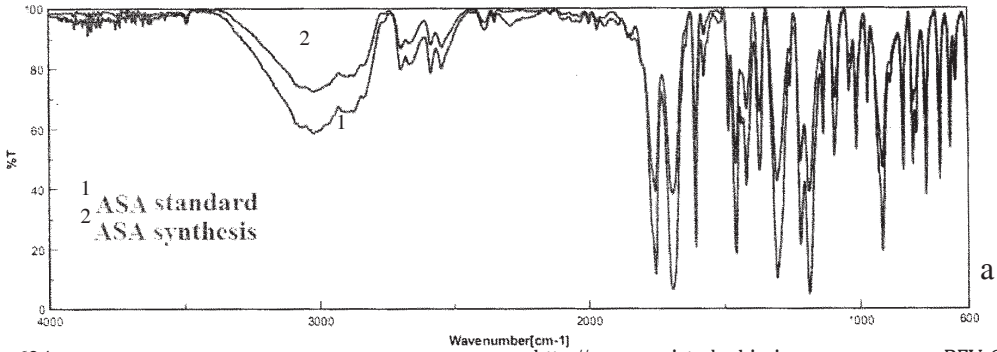


Fig. 2. Reaction schemes for synthesis of ASA and PAR

Both syntheses were carried out in solvent-free medium, namely without using volatile organic compounds. As source of energy, microwave irradiation was used. The main advantages of using microwave irradiation consist in short exposure time, so a quantitative conversion of starting materials (salicylic acid and 4-aminophenol, respectively) was achieved in short periods of time. According to this, a yield of 81.6% for ASA and 92.4% for PAR were achieved during 3 min and 2 min of irradiation, respectively. Literature mentions for the synthesis of ASA, a mean time of 130 min [17], while for PAR 10 min [19], with comparable yields.

The formation of the desired products was monitored by TLC and FTIR spectroscopy. Thin layer chromatography is a useful tool for quickly monitoring the advance of a reaction. In this case, thin layer chromatography (with ethyl acetate as the mobile phase) revealed that ASA obtained from synthesis is pure and does not require recrystallization (TLC one spot, R_f=0.46), while for PAR, two spots are shown on the chromatogram (R_f=0.24 and



a

Fig. 3a. Comparative FTIR spectra for standard and synthesized ASA

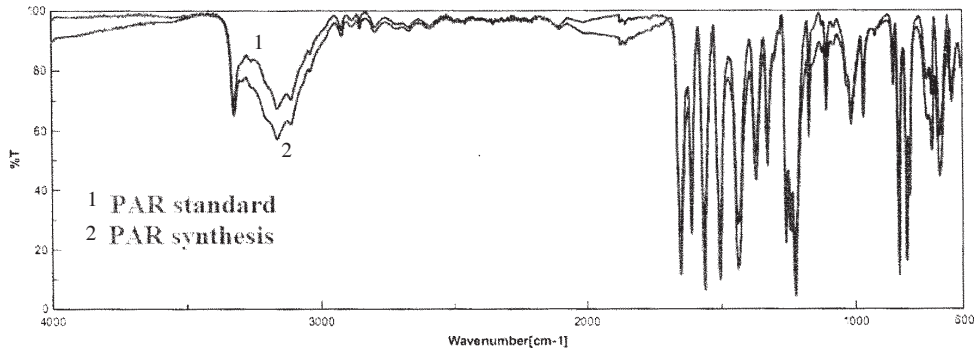


Fig. 3b. Comparative FTIR spectra for standard and synthesized PAR

R_f=0.22(trace)). Comparative TLC for crude PAR, standard PAR and precursor 4-aminophenol, revealed that the spot corresponding to R_f=0.24 is represented by PAR, while the one corresponding to R_f=0.22 is attributed to 4-aminophenol. The purification of crude PAR was realised by recrystallization from hot water (25 mL, 90°C). The recrystallized PAR showed on TLC analysis a singular spot with R_f=0.24.

In order to evaluate and confirm the purity and identity of synthesized ASA and PAR, comparative FTIR spectra were drawn up (fig. 3). The utility of FTIR spectroscopy in drug analysis and synthesis was described in some previous papers [24-37].

FTIR spectroscopy confirmed both purity and identity of ASA and PAR, by the superposition of spectra with the ones drawn up for standards. The corroboration of the results from m.p. and the ones obtained from FTIR spectroscopy revealed both that our synthetic route is a simple and fast one, and the analysis tool are as well simple and reproducible.

Conclusions

This study was realised in order to evaluate the synthesis of two common active pharmaceutical ingredients, namely aspirin and paracetamol using non-conventional route of synthesis, i.e. solvent-free synthesis and energy from microwave irradiation. It was proven that in short time of irradiation (2 and 3 min , respectively) a conversion of starting precursors into bioactive molecules took place with a yield of 81.6% for ASA and 92.4% for PAR. The study confirmed that microwave synthesis is a fast, cheap and clean method that can be successfully used for synthesis of both acetylsalicylic acid and N-acetyl-p-aminophenol.

Acknowledgements: This work was supported by a grant from the University of Medicine and Pharmacy "Victor Babeş" Timişoara (Grant II-C2-TC-2014-16498-08 to Ionuţ Ledeţi).

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Manuscript received: 19.12.2013