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Microwave-assisted conditions for the green synthesis of thioacetamide. Optimization of reaction parameters using response surface methodology

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ABSTRACT

An optimized method for the synthesis of thioacetamide (TA) in relation to the consumption of materials and energy, which reduces the production of waste and minimizes costs, is hitherto presented. The most important highlight of this work is the use of an inexpensive and readily accessible reactant for the thionation process (i.e. phosphorus pentasulfide, P_4S_{10}), combined with both alumina as solid support and a non-conventional microwave (MW) irradiation technique. In addition to this, Response Surface Methodology (RSM) was used to optimize the entire procedure of the synthesis for simultaneous tripled-maximization of Yield (ε), Mass Intensity (MI) and Mass Productivity (MP). Acetamide (AC)/P_4S_{10} molar ratio, time and temperature of reaction were chosen as independent variables; while ε, MI and MP were chosen as responses. The determination of these green metrics parameters allow to evaluate the sustainability of the reaction and compare with other methodologies. A quadratic regression model was derived with satisfactory prediction. Tripled optimization with desirability function predicts a maximum ε of 100%, maximum MI of 29.00 kg/kg and a maximum MP of 3.45% under the following experimental conditions: AC/P_4S_{10} molar ratio of 2.10, time of irradiation of 14 min and a temperature 140 °C.

1. Introduction

The chemistry of organosulfur compounds has been important not only for the wide variety of reactions in which they can participate, but also for many significant biological properties (Block, 1978). The development of convenient and practical methods for the preparation of thioamides is a recent new goal because they have become increasingly useful in organic synthesis (Polshettiwar and Kaushik, 2004), they are included in the preparation and development of peptides and protein chemistry (Polshettiwar and Kaushik, 2006b) and play important roles in reactions of regio- and stereo-selective heterocyclization (Jagodziński, 2003).

Thioamides, which are an important constituent of many biologically active compounds, are a relatively conservative replacement of the amides but differing in its electronic properties, hydrogen-bonding capacity, and photoreactivity (Polshettiwar and Kaushik, 2006b).

In particular, thioacetamide (TA, $CH_3C(S)NH_2$) has numerous applications, as it can be used as organic solvent in the leather, textile and paper industries; as an accelerator in rubber vulcanization, as a motor fuel stabilizer, among others ((IARC), 1974). In addition, it serves as a substitute for hydrogen sulphide in the synthesis of organic and inorganic compounds (Jue and Huyck, 1962) and as a source of sulphide anions in the qualitative analysis of solutions with metal ions (Ni, Pb, Cd, Hg, among others). The main importance is its use as a reagent in different types of heterocyclic synthesis. The preparation of thiazoles, thianthrene and spiroheterocyclic compounds may be mentioned as examples. Also, TA is used as a precursor of sulphur in the preparation of nanoparticles of metal salts, as for example of "microrods" of FeS_2 (He et al., 2006).

The first register of the synthesis of TA was made by Kindler and Dehn (1921) by the reaction of ammonium acetate and aluminium sulphide. However, in the process of thionation of carbonyl compounds, a wide variety of reagents including S_8 (elemental sulphur) (Pedersen and Lawesson, 1979), CS_2, R_3OBF_4/NaSH, R_2PSX (Pedersen and Lawesson, 1977), $(Et_2Al)_2S$, P_2S_5/Na_2CO_3 (Ashraf Shalaby et al., 1996), P_4S_{10} (Schmidt et al., 1959), Lawsson's reagente (Cava and Levinson, 1985; Pedersen and Lawesson, 1979) and P_4S_{10}/HMDO (hexamethyldisiloxane) (Curphey, 2000, 2002) have been evaluated. In recent years Lawsson's reagent (LR) and a combination of P_4S_{10}/HMDO have replaced P_4S_{10} as the reagent of choice for many thionation methods (Polshettiwar and Kaushik, , 2004, 2006a, 2006b). However, besides its high cost, LR results in the formation of by-products derived from the reagent itself which cannot be easily removed by an extractive procedure and require chromatography, making the method more expensive

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(Polshettiwar and Kaushik, 2006a). The combination of P_4S_{10}/HMDO (known as Curphey's thionation reagent), is good in terms of reactivity but the use of HMDO makes the method expensive and the by-products formed need to be removed by column chromatography (Polshettiwar and Kaushik, 2004).

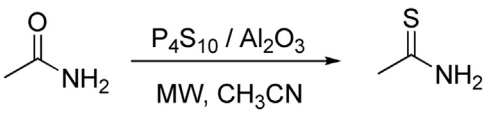
Taking into account that one substantial area of current green research is the use of microwave irradiation for efficient heating of reaction mixtures (Herrero et al., 2008), we decided to perform the thionation synthesis reaction employing this technology. The heating or incorporation of energy by microwave radiation shows significant improvements over conventional methods (electric plates or baths of oils) according to the fundamentals of Green Chemistry since it complies with the ecological, selective, clean, controlled, fast and versatile advantages (de la Hoz and Loupy, 2013).

Among the great offer of reagents for the conversion of amides to thioamides, we have used the readily accessible and inexpensive P_4S_{10} on a solid support (alumina), which has also been used in organic chemistry for many years (Polshettiwar and Kaushik, 2004). Such reagent helps simplifying the purification processes, because it may be removed from any solution by simple filtration. Since chemical production increases every day, efforts into environmental protection, "greener" materials and processes should play a central role. Therefore, this method is advantageous in terms of the use of inexpensive reagents, simple reaction processes, and cleaner products. A similar procedure was reported for the synthesis of thioamides giving good yields, but with an average reaction time of 9 h (Lagiakos et al., 2011). Besides, Polshettiwar et al.(Polshettiwar and Kaushik, 2006b) obtained TA (78% yield) from AC (P_4S_{10}/Al_2O_3 in acetonitrile) but with reflux for 6 h. The authors suggest that the increment in yield (in comparison with P_4S_{10} alone which is 70%) is due to the presence of the catalyst.

In addition to the advantage of the use of a solid support and microwaves, the optimization of the experimental operating parameters (synthesis conditions) is other interesting matter, from the green point of view (See Scheme 1). It is possible to decrease the number of experimental tests, if the range of parameter's values (for which the highest yields will be obtained) is known beforehand. Thus, Response Surface Methodology (RSM) was applied to the system, because this methodology is widely adapted for optimization of various parameters in synthesis (Bhalkar et al., 2015; Ferdosian et al., 2014; Nandiwale et al., 2015; Nguyen et al., 2017). Application of RSM to study the insights of the influence of different parameters in the microwave induced synthesis of TA with P_4S_{10}/Al_3O_2, has not been reported so far.

In summary, this study explores new avenues on uses of microwave irradiation and optimization of synthesis by using RSM for the efficient production of Thioacetamide. The Yield and the two most relevant green metrics parameters, namely Mass Intensity (MI) and Mass Productivity (MP), were evaluated as responses against the three critical parameters, namely reagents molar ratio, time and temperature. Besides, the desirability function for optimization of the overall process was employed in order to develop an efficient method for achieving maximum yield of thioacetamide production and the most favourable green conditions, by a combination of all optimized input factors. An optimized response model was proposed. The most favourable parameters obtained from the RSM were validated by experiments.

As far as we know, there are no reports in the bibliography about the green parameters' calculations for the thionation reaction, until now. Therefore, this is an innovative work on the green chemistry field.



Scheme 1. Thionation reaction studied.

2. Experimental details

2.1. Chemicals

Acetamide (AC), P_4S_{10} and Al_2O_3 were commercially available. The purity of these reagents was confirmed by mass spectrometry; IR and/or NMR (see Supporting information). Reagents were used without further purification. All reagents were purchased from Sigma-Aldrich and the solvent (acetonitrile) although of high purity, purified by distillation and kept dry using sodium sulphate.

2.2. Equipment

The synthesis reactions were performed in a microwave reactor Antor-Paar MonoWave 300, with 10 mL vials. The temperature and time of reaction were varied according to each experience, with constant stirring of 1200 rpm.

The CG-Mass spectra were carried out in a Shimadzu GC-MS-QP 5050 spectrometer, equipped with a VF (30 m × 0,25 mm × 5 μm) capillary column, using 1,1 mL/min of He as carrier, injector temperature of 280 °C, and a ramp heating of 10 °C/min (40–100 °C); though higher temperatures were tried without appearance of side byproducts. The mass spectrometry recordings were made in Electron Impact mode (EI) at ionization energy of 70 eV.

The infrared spectra were recorded at room temperature, with a Bruker IFS-28 spectrometer, in the range 4000–400 cm^{-1}. The spectra were recorded from solid samples in KBr pellets (spectral resolution 2 cm^{-1}).

2.3. Methods

2.3.1. Preparation of thioacetamide

TA was prepared from AC, using P_4S_{10}/Al_2O_3 in 2 mL of acetonitrile as solvent, under microwave irradiation with stirring and air cooling. Alumina and by-product compounds were eliminated from the mixture of reaction by filtration. The yield of the desired product, that indicates the completeness of the reaction, is defined in the Supporting information.

2.3.2. Preparation of samples

0.5 mL of the reaction crude was taken and diluted in 2 mL of acetonitrile. After homogenizing for 10 s, 0.5 μL of the diluted solution was injected into the CG-MS.

2.3.3. Green metrics

The different green parameters allow defining the efficiency and sustainability of a synthesis and the general quality of a process. The efficiency of a process not only depends on the product of the synthesis, but also the formation of waste. Over the last few years, efforts have been made in order to unify reaction metrics, because many ways to quantifying ecological processes and products have been proposed.

2.3.3.1. Green Star. Green Star is a semi-quantitative environmental parameter which is used for the overall sustainability assessment of a chemical reaction. It allows evaluating the benignity of a process, and comparing different alternative experimental procedures with a simple visual analysis, to choose the best reaction conditions and to improve synthesis protocols based on the 12 Principles of Sustainable Chemistry (Anastas and Warner, 1998). This objective is achieved by evaluating the sustainability of the reaction for each principle, on a scale from 1 to 3 for the maximum value, based on pre-defined criteria and representing the results in a radial graph (P. Dicks and Hent, 2015).

2.3.3.2. EcoScale. This parameter is a powerful tool to compare several preparations of the same product, based on safety, economic and ecological features. The EcoScale is a semiquantitative tool to