



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

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ARTICLE INFO

Keywords:
Thionation
Thioacetamide
Microwave-assisted synthesis
RSM factorial design

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), Lawesson's reagent (Cava and Levinson, 1985; Pedersen and Lawesson, 1979) and $P_4S_{10}/HMDO$ (hexamethyldisiloxane) (Curphey, 2000, 2002) have been evaluated. In recent years Lawesson'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).

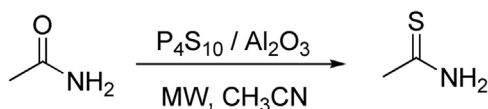
Taking into account that one substantial area of current green research is the use of microwave irradiation for efficient heating of reaction mixtures (Herrero et al., 2008), we decided to perform the thionation synthesis reaction employing this technology. The heating or incorporation of energy by microwave 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_2O_3 , 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 semi-quantitative tool to

evaluate the quality on a laboratory scale. The highest rank in the EcoScale (100 points) refers to 'ideal' reaction that has a 100% yield, uses inexpensive reagents, is conducted at room temperature, and is safe for both the operator and the environment. If the parameters of a real synthesis differ from 'the ideal value', penalty points are assigned, lowering the total score by certain values that have been proposed by Van Aken et al. (Tobiszewski et al., 2015). The EcoScale value allows selecting different preparations according not only to their greenness, but also to their costs. When the EcoScale value is greater than 75, the process or reaction is considered "excellent", between 50 and 75 is considered "acceptable" and less than 50 "unacceptable". The main disadvantage of the EcoScale evaluation is that it does not provide information about the type of hazards, it only gives a score.

2.3.4. Mass metrics parameters

Parameters such as yield (ϵ), stoichiometric factor (SF), Atom Economy (AE), Carbon Efficiency (CE), Environmental Factor (E-Factor), Material Recovery Parameter (MRP) and Reaction Mass Efficiency (RME) are defined in the Supporting information.

2.3.4.1. Mass Intensity (MI). MI takes into account the efficiency of the reaction, its stoichiometry, the amount of solvents, all the reagents and auxiliary substances that have been used in the synthesis and purification. It is calculated as follows:

$$MI = \frac{\text{total mass used in the process (kg)}}{pz \text{ (kg)}}$$

2.3.4.2. Mass Productivity (MP). This parameter is calculated as $1/(MI)$, and highlights the use of resources. For example, a MP of 1.5% in a synthesis indicates that 98.5% of the total mass used as reagent is being wasted.

Andraos has proposed a general algorithm for the evaluation of mass incorporation efficiency (characteristic for each process and known as "materials usage footprint"), which consists of representing these different parameters in each vertex of a pentagon (radial graph). A value of zero is assigned to the center of the figure and 1 to the vertices (maximum value). Each vertex is represented with a different metric and the ideality is reached when the metrics coincide with the perimeter of the figure.

2.3.5. Analytical procedure

Design-Expert 7.0.0 software (Stat-Ease, Inc., Minneapolis, USA) was employed to generate a total of 15 experimental designs, including 12 factorial experiments and 3 replicates at central point. The same software was also used to the statistical analyses, and regression models. The adequacy of the developed models were tested by performing analysis on coefficient of determination (R^2), adjusted coefficient of determination (R_{adj}^2) and predicted coefficient of determination (R_{pre}^2), and its statistical significance was checked by a Fisher F-test. The level of significance was given as values of the probability less than 0.05.

2.3.6. Experimental design

The response surface methodologies (RSMs) consist on a group of empirical techniques devoted to the evaluation of existing relationships between a cluster of controlled experimental factors and measured responses according to one or more selected criteria (Bezerra et al., 2008). Box and Behnken (Box and Behnken, 1960) suggested how to select points from the three-level factorial arrangement, which allows the efficient estimation of the first- and second-order coefficients of the mathematical model. These designs are, in this way, more efficient and economical than their corresponding $3k$ designs, mainly for a large number of variables. In Box-Behnken designs (Costa Ferreira et al., 2007; Otto, 1999), the experimental points are located on a

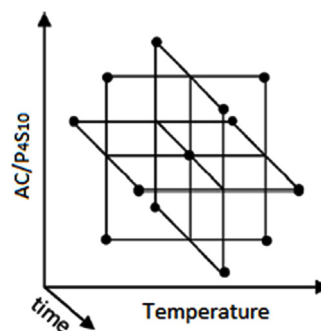


Fig. 1. Box-Behnken design for the three factors of the experiment.

Table 1

Matrix of variables and their employed levels in the Box-Behnken design.

Parameters	Symbol	Code levels		
		- 1	0	1
AC/P ₄ S ₁₀ molar ratio	A	2	3	4
Reaction temperature	B	60	105	150
Reaction time	C	1	8	15

Table 2

Selected values for the construction of the "Green Star" according to Green Chemistry Criteria.

Principles of Sustainable Chemistry	TA	Principles of Sustainable Chemistry	TA
P1 – Prevent waste	2	P7 – Use of Renewable Feedstocks	2
P2 – Atom Economy	2	P8 – Reduce Derivatives	2
P3 – Less Hazardous synthesis	1	P9 – Catalysis	3
P4 – Design Benign Chemicals	–	P10 – Design for Degradation	3
P5 – Benign Solvents and Auxiliaries	2	P11 – Real-Time Analysis for Pollution Prevention	–
P6 – Design for Energy Efficiency	1	P12 – Inherently Benign Chemistry for Accident Prevention	3

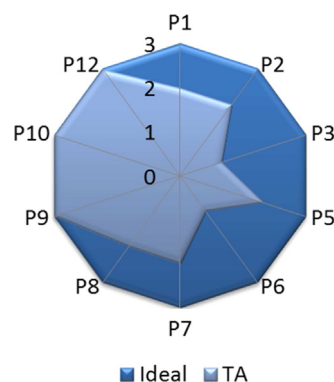


Fig. 2. Green Star.

hypersphere equidistant from the central point, as exemplified for a three-factor design, (Fig. 1).

Its principal characteristics are: (1) Requires an experiment number according to $N = 2k(k - 1) + cp$, where k is the number of factors and (cp) is the number of the central points; (2) All factor levels have to be adjusted only at three levels ($-1, 0, +1$) with equally spaced intervals between these levels.

For three factors (parameters), the Box-Behnken experimental design involves 15 sets of experimental runs, consisting on 12 factorial points and 3 centres. These fully randomized experiment formulations consist on all possible combinations of the independent parameters, at

Table 3
Comparison of EcoScale with the methodology reported in bibliography.

EcoScale		Polshettiwar	Our system
Reaction	Yield	11	0
	Method	2	2
	Time and Temperature	3	2
	Purification	0	0
AC	Cost	0	0
	Security	5	5
P ₄ S ₁₀	Cost	0	0
	Security	5	5
	Cost	0	0
Al ₂ O ₃	Security	0	0
	Total	36%	24%
	EcoScale	64%	76%

all levels. In our case, the optimization process for maximizing the % of yield (ϵ), MP and MI of the TA was carried out taking into account three independent parameters: AC/P₄S₁₀ molar ratio (in a range of 2–4), temperature (between 60 and 150 °C) and time (in a range of 1–15 min) of reaction. The ranges of these three parameters were chosen on the bases of our preliminary experiments, and taking into account literature. The parameters of synthesis were coded into levels – 1, 0 and + 1, and are shown in Table 1.

According to the BBD matrix described (see below in Mass Incorporation Parameters section: Table 4), a second order polynomial model was fitted to experimental results performed on the bases of the experimental designs generated, for predicting the mathematical relationship between the independent factors –i.e. the parameters of synthesis–, and the dependent response. During the optimization process, relationship among responses, main parameters, and interactions can be formulated as a quadratic model, which also includes the linear terms:

$$Y = \beta_0 + \sum_{i=1}^k \beta_i x_i + \sum_{i=1}^k \beta_{ii} x_i^2 + \sum_{i=1}^{k-1} \sum_{j=2}^k \beta_{ij} x_i x_j + \epsilon$$

where Y is the predicted response, β_0 is an offset term, β_i is the coefficient of linear effect, β_{ii} is the coefficient of squared effect, β_{ij} is the coefficient of interaction effect, and ϵ is the random error.

2.3.7. Multiple response optimization

The present work involves simultaneous optimization of multiple responses (ϵ , MI and MP). Therefore, it is important to find out an

Table 4
Independent parameters and sustainable metrics values.

Run N°	Parameters			Mass Metrics ^a								
	A	B ^b	C ^c	ϵ	1/SF	AE	RME (kernel)	RME (Curzons)	RME (Andraos)	MRP	MI (Kg/Kg)	MP (%)
1	2	60	8	0.96	0.80	0.27	0.44	0.35	0.02	0.04	28.66	3.49
2	4	60	8	0.77	0.64	0.27	0.38	0.24	0.01	0.05	36.77	2.72
3	2	150	8	1.00	0.84	0.27	0.43	0.36	0.01	0.04	29.22	3.42
4	4	150	8	0.99	0.85	0.27	0.41	0.35	0.01	0.04	29.80	3.36
5	2	105	1	0.97	0.83	0.27	0.41	0.34	0.01	0.04	31.14	3.21
6	4	105	1	0.78	0.60	0.27	0.39	0.23	0.01	0.05	38.29	2.61
7	2	105	15	1.00	0.79	0.27	0.41	0.32	0.01	0.04	32.11	3.11
8	4	105	15	0.91	0.62	0.27	0.54	0.33	0.01	0.04	30.40	3.29
9	3	60	1	0.84	0.78	0.27	0.35	0.27	0.02	0.06	27.64	3.62
10	3	150	1	0.96	0.69	0.27	0.53	0.37	0.02	0.05	24.60	4.06
11	3	60	15	0.92	0.72	0.27	0.46	0.33	0.02	0.05	25.08	3.99
12	3	150	15	1.00	0.72	0.27	0.55	0.39	0.02	0.04	23.97	4.17
13	3	105	8	0.98	0.70	0.27	0.56	0.39	0.02	0.05	24.26	4.12
14	3	105	8	0.99	0.71	0.27	0.55	0.39	0.02	0.04	24.28	4.12
15	3	105	8	0.98	0.69	0.27	0.53	0.37	0.02	0.05	24.93	4.01

^a ϵ , MI and MP are the responses obtained from the BBD and will be modeled using RSM.

^b B represents temperature (°C).

^c C represents time (minutes).

overall balanced optimum condition by having a compromise between optimum conditions of individual responses. For this, a multicriteria methodology was used for the simultaneous optimization of the significant response variables. The Derringer function (desirability function) is the most currently used methodology to find optimal compromises between the total numbers of responses taken into account (Derringer and Suich, 1980). Each estimated variable response is transformed into a dimensionless individual desirability value (d_i) using the desirability function of the statistical program. The desirability function included the minimum and maximum acceptable values of each response. The values of d_i vary in the interval $0 \leq d_i \leq 1$, increasing as the desirability of the corresponding response increases. This transformation makes it possible to combine the results obtained from responses localized in different regions because they were measured on different orders of magnitude. The individual desirability was then combined to give an overall desirability (D) by using a geometric mean equation:

$$D = \sqrt[m]{d_1 d_2 \dots d_n}$$

where m is the number of responses studied in the optimization process.

The simultaneous optimization process aimed to find the levels of the factors that demonstrated the maximum overall desirability.

3. Results and discussion

3.1. Structural characteristics

The structure of TA was analyzed using mass spectrometry and IR spectroscopy. The most relevant ions are: $m/z = 75$ (molecular ion); $m/z = 60$ and 59 , corresponding to the loss of CH_3 and NH_2 from the molecular ion, respectively; and $m/z = 42$, belonging to the M-.SH ion.

FTIR (KBr): 3295 (ν_{aNH}), 3080 (ν_{sNH}), 2977 (ν_{aCH}), 2945 (ν_{sCH}), 1650 ($\delta_{\text{NH}_2} + \nu_{\text{CN}}$), 1390 ($\nu_{\text{CN}} + \delta_{\text{aCH}_3}$), 1361 (δ_{sCH_3}), 1303 ($\nu_{\text{NH}_2} + \nu_{\text{CC}} + \nu_{\text{CS}}$), 1025 ($\nu_{\text{CH}_3} + \nu_{\text{NH}_2} + \delta_{\text{aCH}_3}$), 972 ($\nu_{\text{NH}_2} + \nu_{\text{CC}} + \nu_{\text{CS}}$), 760 (ν_{NH_2}), 719 ($\nu_{\text{CS}} + \nu_{\text{CC}}$), 460 ($\nu_{\text{CS}} + \delta_{\text{NCS}}$) cm^{-1} .

Table 2 shows the value calculated for the construction of the "Green Star", in the synthesis of TA using pre-established criteria. The corresponding radial graph is shown in Fig. 2. The degree of sustainability of the process is in light blue color. Note that the ideal sustainable process is that which occupies the entire area of the figure (in blue). It also should be noted that the 4th and 11th principles are not calculated because no new compound is prepared.

Table 3 shows the penalty points for each of the 6 general

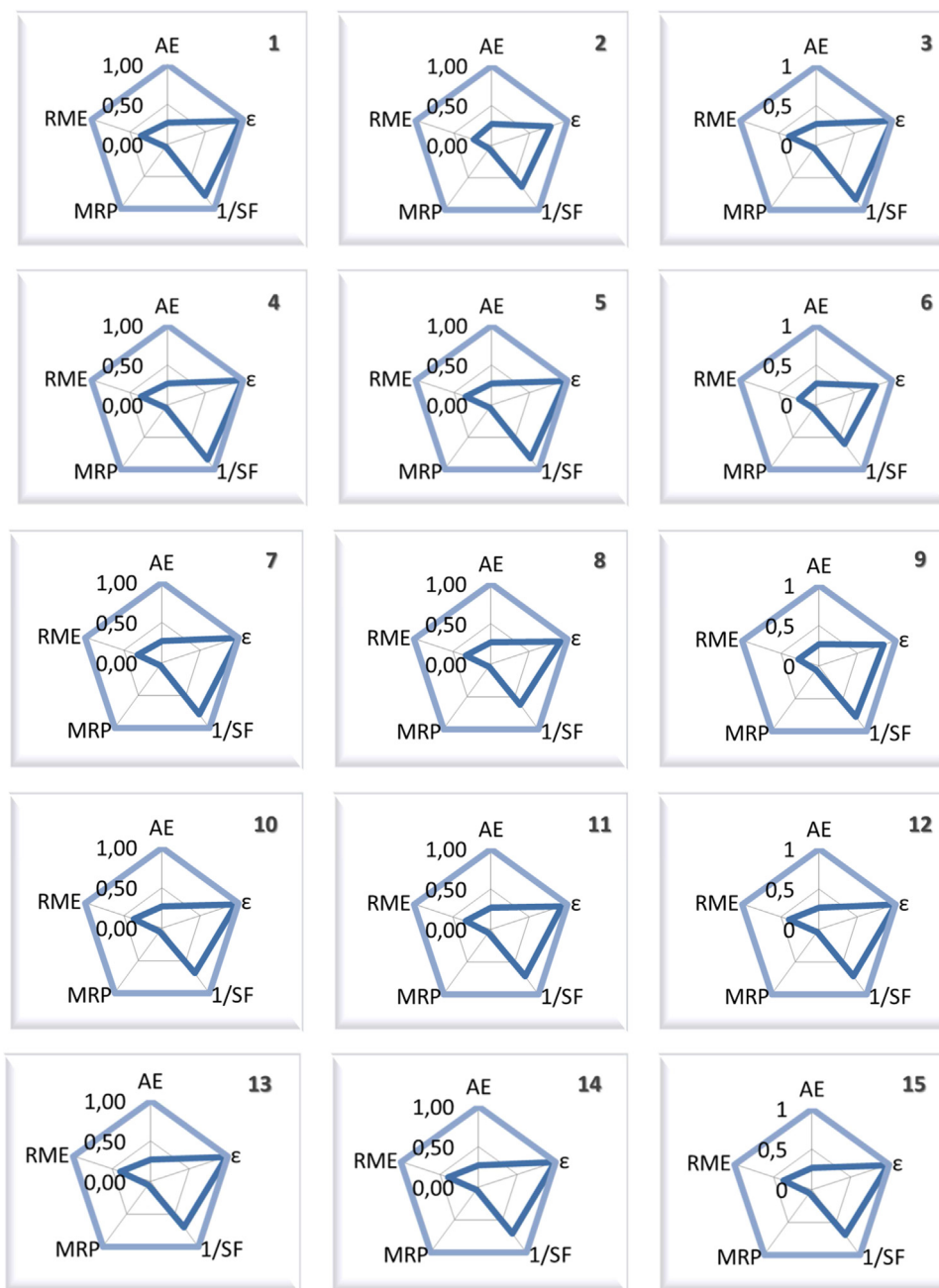


Fig. 3. Radial graphs of the 15 experimental runs from Table 4 and for some mass metrics.

parameters that influence the quality of the reaction conditions, comparing at the same time our system and that of the traditional synthesis by Polshettiwar. The values for each of these parameters are shown.

Our proposed system, with an EcoScale value > 75, is classified as “excellent” while that reported by Polshettiwar, as “acceptable” since it has a value between 50 and 75. This classification applies for reactions with product purity of at least 98%.

3.2. Mass incorporation parameters

Table 4 shows the yields and mass metrics for each of the 15 reactions performed under the given conditions of molar ratio (A), temperature (B) and reaction time (C) requested by the experimental Box-Behnken model.

From the values reported in Table 4 and the analysis of the following spider charts, it can be seen that AE and MRP did not vary

significantly, taking values of 27%, and 4–5%, respectively. Low values for AE are typical of substitution reactions, while addition or rearrangement reactions are favored with high values. Regarding MRP, not significant variation is observed since the type and amount of recovery materials are the same (varies little because it depends on the ϵ and pz).

Fig. 3 shows the different spider charts and the conditions that improve or worsen the sustainability of the process. RME can be analyzed using these graphs because it is related to all the metrics represented. SF is evaluated by consideration of the molar ratio.

3.3. Model building and analysis of variance (ANOVA)

Based on the Box-Behnken design, the 15 recommended runs were carried out with the yields shown in the fifth column of the Table 4. These results demonstrate that the yield changes with the variation of

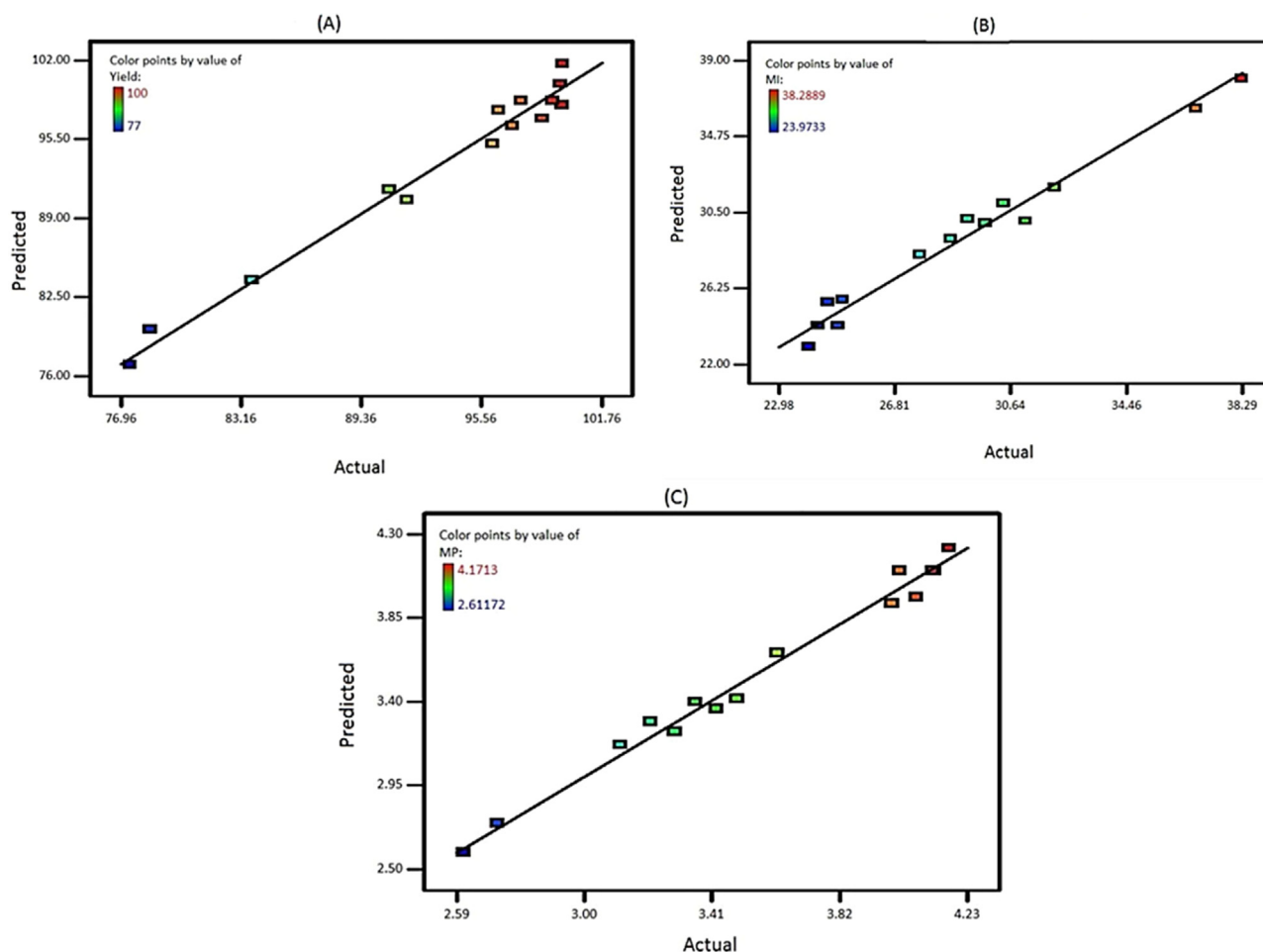


Fig. 4. Actual vs predicted values of the regression for ϵ (A), MI (B) and MP (C).

Table 5
Statistics summary for response surface reduced quadratic model.

Response	<i>p</i> -value (Model)	R^2	R^2_{adj}	R^2_{pred}	CV	<i>p</i> -value (LOF)
ϵ	0.0002	0.9794	0.9521	0.7934	1.8	0.1972
MI	< 0.0001	0.9793	0.9587	0.8607	3.2	0.1188
MP	< 0.0001	0.9860	0.9719	0.9114	2.4	0.3392

R^2 , determination coefficient; R^2_{adj} , adjusted determination coefficient; R^2_{pred} , predicted coefficient; CV, coefficient of variation; LOF, probability for lack of fit.

the synthesis conditions. As an example, at the lowest temperature of reaction (60 °C), the highest yield (96.5%) is reached for a molar ratio of 2; while the lowest yield (77.4%) is obtained at a molar ratio of 4. It is important to mention that the MP values are in accordance with the trend observed in ϵ . Thus, when the yield obtained is the highest (99.8%), the MP value is also the highest (4.17). Briefly, all the results indicate that AC concentration is one of the most relevant parameters of the reaction. With this in mind, the BBD was applied to optimize the experimental conditions and to probe the effects that AC/P₄S₁₀ molar ratio, reaction temperature and reaction time parameters have on yield, MI and MP.

The responses were treated with linear, quadratic and cubic model functions to find the best fitting model, being finally the quadratic model the best one. For all of the trials, coefficients with *p*-values lower than 0.05 were considered to have a statistically significant effect on the responses. Otherwise, their influence would be insignificant and were therefore removed from the regression model. The empirical relationship between ϵ , MI and MP and the three test variables obtained

by the application of BBD is given by:

$$\epsilon(\%) = 98.70 - 5.95A + 5.61B + 3.31C + 4.53A*B + 2.45A*C - 3.47A^2 - 2.18B^2 - 3.68C^2$$

$$MI(\text{Kg/Kg}) = 24.17 + 1.76A - 1.32B - 1.26C - 1.88A*B - 2.21A*C + 7.18A^2 + 1.39C^2$$

$$MP(\%) = 4.10 - 0.16A + 0.15B + 0.13C + 0.18A*B + 0.19A*C - 0.87A^2 - 0.16C^2$$

where A is the coded value of AC/P₄S₁₀ molar ratio, B is the coded value of reaction temperature and C is the one for the reaction time. Positive terms indicate a synergistic effect on the responses, while negative ones point out to an antagonistic effect. It should be noted that polynomial models are reasonable approximations of the true functional relationship over relatively small regions of the entire space of the independent variables. Fig. 4 shows predicted versus actual data values. The clustering of points around the diagonal line indicates a satisfactory correlation for ϵ (Fig. 4.a), MI (Fig. 4.b) and MP (Fig. 4.c), thus confirming the robustness of the model.

The built model for the yield of thionation shows all type of terms including linear, quadratic and interaction factors as significant, and therefore it appears as rather complex.

To evaluate the validity and suitability of the regression models, the analysis of variance (ANOVA) and the F-test were applied. The statistics summary results for the ϵ , MI and MP of the reaction are presented in Table 5. Statistical analysis shows that the *p*-value of the model (see Table 5) is lesser than 0.05, which confirms its significance and

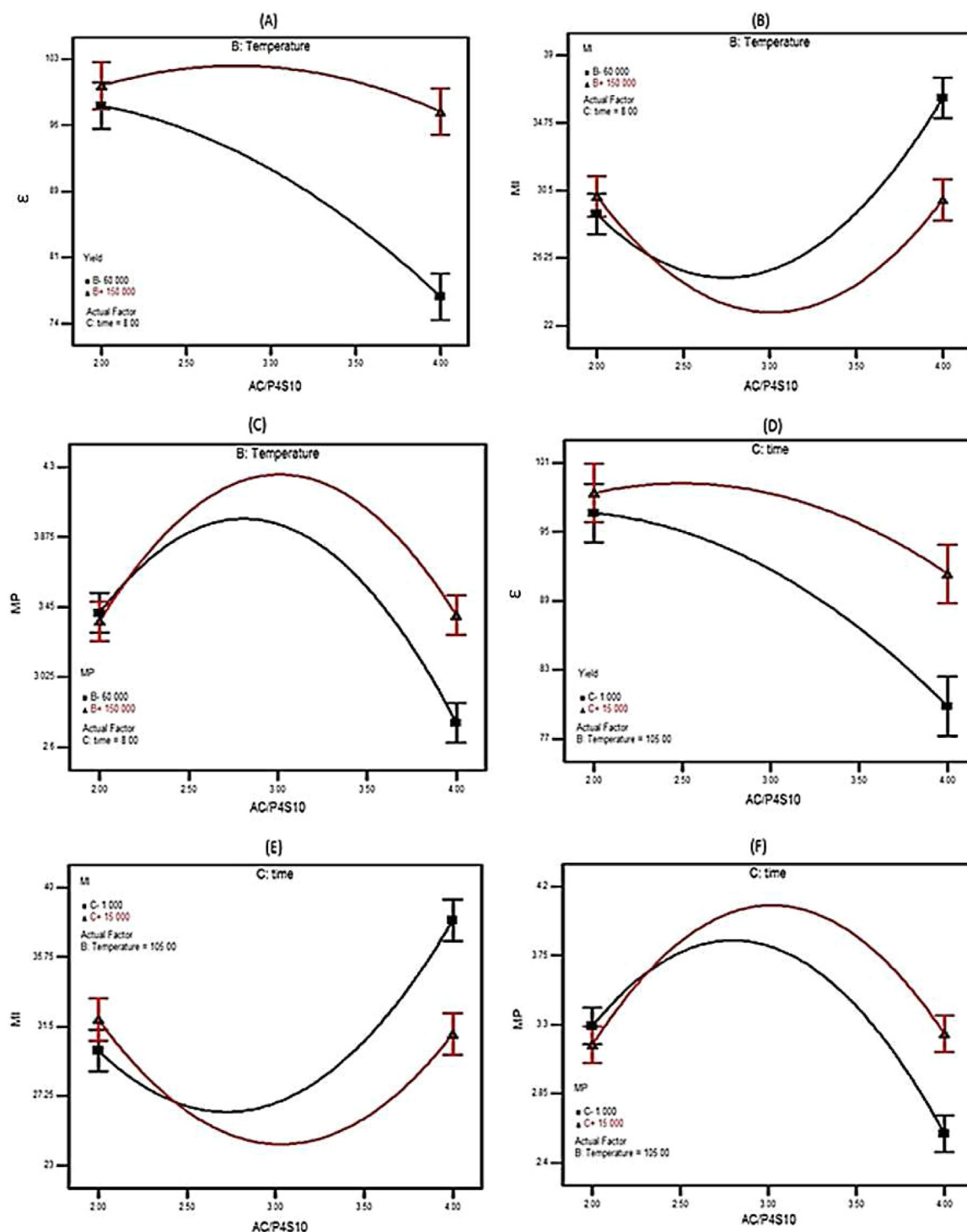
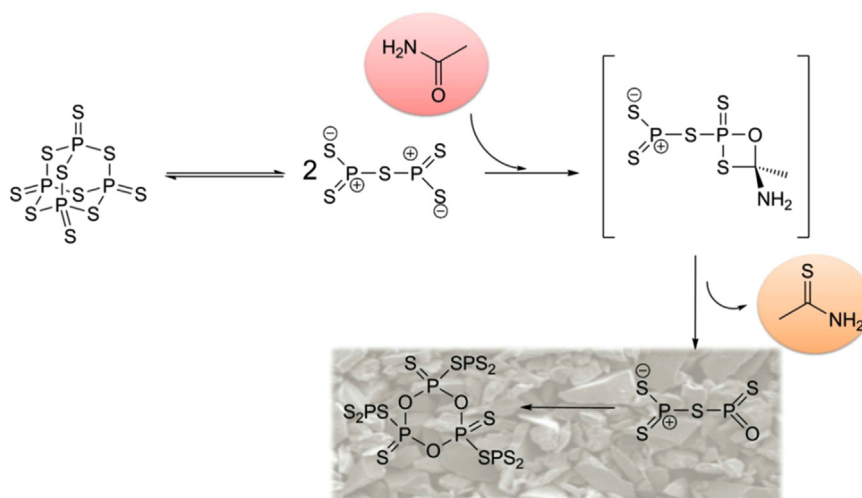


Fig. 5. Interaction plots of the effect of the different parameters on the synthesis of TA: AC/P4S10 molar ratio and reaction temperature for ϵ (A), MI (B) and MP (C); AC/P4S10 molar ratio and reaction time for ϵ (D), MI (E) and MP (F).

desirability for the prediction.

The “lack of fit” is not significant (p -value greater than the confidence interval). This non-significant “lack of fit” is desirable because it can be used as a tool to confirm the good fit of the model. The goodness of the model can be checked by the coefficient of determination (R^2) as well. R^2 is a measure of the amount of variation around the mean explained by the complete model and R_{adj}^2 is the corresponding amount adjusted for the number of terms included. The R_{adj}^2 decreases as the number of terms in the model increases if those additional terms do not add value to the model. On the other hand, R_{pred}^2 is the response for new

data. In general, it is accepted that the R_{pred}^2 and the R_{adj}^2 should be within 0.20 of each other to be in reasonable agreement. Otherwise, there may be a problem with either the data or the model. The coefficients of determination (R^2) for the TA yield, MI and MP are very high, indicating that over 97.94%, 97.93% and 98.60% of variations of the yield can be explained by the three independent variables, respectively. The values of the R_{adj}^2 are a bit lower than R^2 , again demonstrating the significance of the model and indicating that it is not over-fitted. Furthermore, the predicted R_{pred}^2 of 0.7934, 0.8607 and 0.9114 respectively, demonstrate a good agreement between the predicted values



Scheme 2. Reaction Mechanism Scheme.

of the fitted model and the actual experimental values. The coefficient of variation (CV) can be considered reasonably reproducible if the CV is < 10%. In the present models, smaller values of the coefficient of variation (1.8–3.2%) implied that the models possessed a superior accuracy and the experiments performed were reliable.

Fig. 5 shows the relationship between ϵ , MI and MP as a function of the molar ratio AC/P₄S₁₀, at the selected extreme temperatures (low and high) (Fig. 5A, B and C) and at the selected extreme times (Fig. 5D, E and F). It is possible to observe that at low molar ratios, ϵ , MI and MP are independent of temperature and/or reaction time. However, when the ratio increases, the increase in either temperature or time favors the performance of the reaction (ϵ), but not MI and MP. This fact could be understood because of the availability of other reaction channels, at higher temperatures, that provide extra sulphur atoms to the acetamide in a step-wise reaction. This, in turn, could also explain why at longer times the result goes in the same direction.

For a similar system, which uses LR as thionating agent (Scheme 2), it is assumed that once P₄S₁₀ is cleaved, the P₂S₅ species becomes anchored to the solid support, allowing it to be readily available for the first step of the reaction, which begins with the nucleophilic attack of the C=O group of acetamide on the phosphorus atom lacking density charge. In this step, the conversion of AC to TA would only depend on the availability of P₂S₅. In addition, it was observed that the thionation yield using the combination of P₄S₁₀/Al₂O₃ (solid supporting agent) is higher than using P₄S₁₀ only^{2,37}.

The by-products of the reaction –i.e. the highly condensed polythiophosphates– are potent electrophiles capable of promoting undesirable side reactions on both the carbonyl and thiocarbonyl derivatives (Polshettiwar and Kaushik, 2006b). However, the solid Al₂O₃ binds to these highly electrophilic species and scavenges them, thereby raising the yield of the reaction. Thus, the beneficial effect of Al₂O₃ is basically due to the anchoring of yield-lowering intermediates formed during the course of the reaction.

3.4. Most favourable parameters

Figs. 6 and 7 show two-dimensional contour plots. Each contour curve represents the test of two variables with the third maintained constant in its central value. It is reported (Bhalkar et al., 2015; Nandiwal et al., 2015) that circular contours denote a non-significant interaction between the corresponding variables, while elliptic contours symbolize significant interactions between the related parameters. The combined influence of temperature and molar ratio (6-a, -b and -c), and time and molar ratio (7-a, -b and -c) are indicated by outline strokes. The contour plot for temperature and time are shown in the S.I. (Fig.

S49)

The interaction between the molar ratio and the reaction temperature (AB), at a reaction time of 8 min, is shown in Fig. 6-a, with the yield as response. The interaction effect in AB is confirmed by the low *p* value (0.0023) (see Table S16). This is also evidenced by the elliptic shape of the contour curves. It can be clearly seen that at low temperatures, ϵ is maximum at low ratios, and when the molar ratio increases, ϵ decreases; while at high temperatures the model predict a high yield practically independent of the molar ratio. In Fig. 6-b and -c the elliptic forms of the contour curves are evident as a consequence of a significant interaction between A and B with *p* values of 0.0065 and 0.0083, respectively (see Table S17). Note that the central region of the plots show, the maximum values for MP (6-b) and therefore the minimum values for MI regardless of the temperature.

A similar analysis could be performed for the data sets of the molar ratio and the reaction time (A, C), at a constant temperature of 105 °C, where the maxima can be observed in the upper left area, in the middle zone and in the lateral regions for ϵ Fig. 7-a, MP, 7-b and MI 7-c, respectively.

With increasing reaction time and temperature (BC) at a constant molar ratio, ϵ and MP also increase, while MI decreases (shown in S.I. Fig. S49). It is found that the interaction between temperature (B) and reaction time (C) is not significant within the range of experimental values for 95% confidence with values *p* 0.229, 0.3302 and 0.1569 for ϵ , MP and MI respectively (see Table S18). From this study, we find that the molar ratio is the most important term, while temperature and reaction time are less significant. The interaction between temperature and time does not present synergy on the responses, in the range of experimental values chosen.

3.5. Process optimization

It should be noted that the role of optimization is to find a good set of conditions that will meet all the goals, which are combined into an overall desirability function. Desirability is an objective function that ranges from zero outside of the limits to one and is an adjustable parameter that the program seeks to maximize. By starting from several points in the design space, chances for finding the best local maximum are high. In this study, optimization was based on the simultaneous maximization of yield, MI and MP. The optimum conditions proposed by the model were AC/P₄S₁₀ molar ratio of 2.10, time of irradiation of 14 min and a temperature 140 °C, with which ϵ of 100%, MI 29.00 kg/Kg and MP 3.45% were achieved.

Fig. 8 shows the surfaces of the desirability function for the different parameters. It can be seen that the maxima are found at a low ratio for

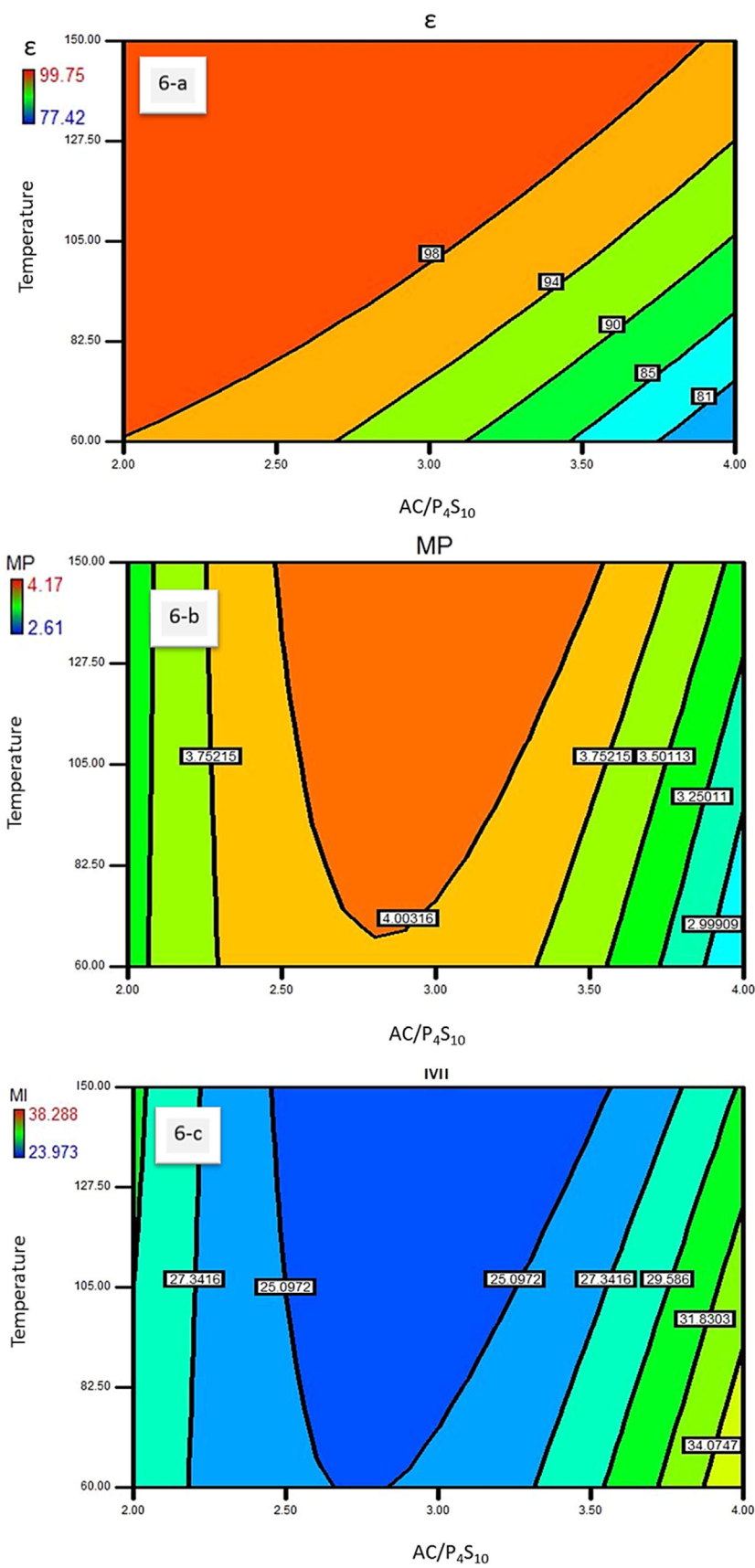


Fig. 6. Contour plots of the effect of AC/P₄S₁₀ molar ratio and reaction temperature on ε (a), MP (b) and MI (c).

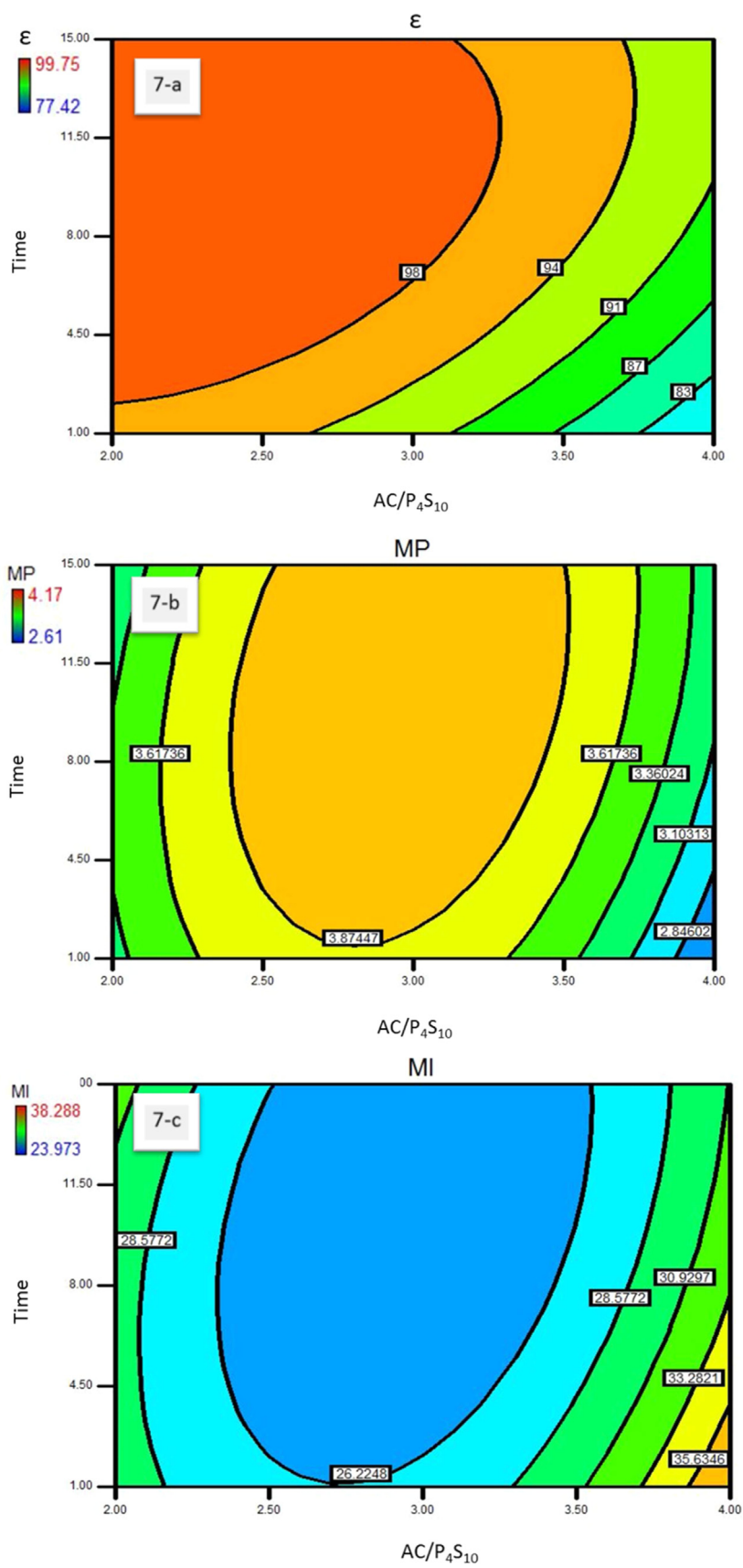


Fig. 7. Contour plots of the effect of AC/P₄S₁₀ molar ratio and reaction time on ε (a), MI (b), and MP (c).

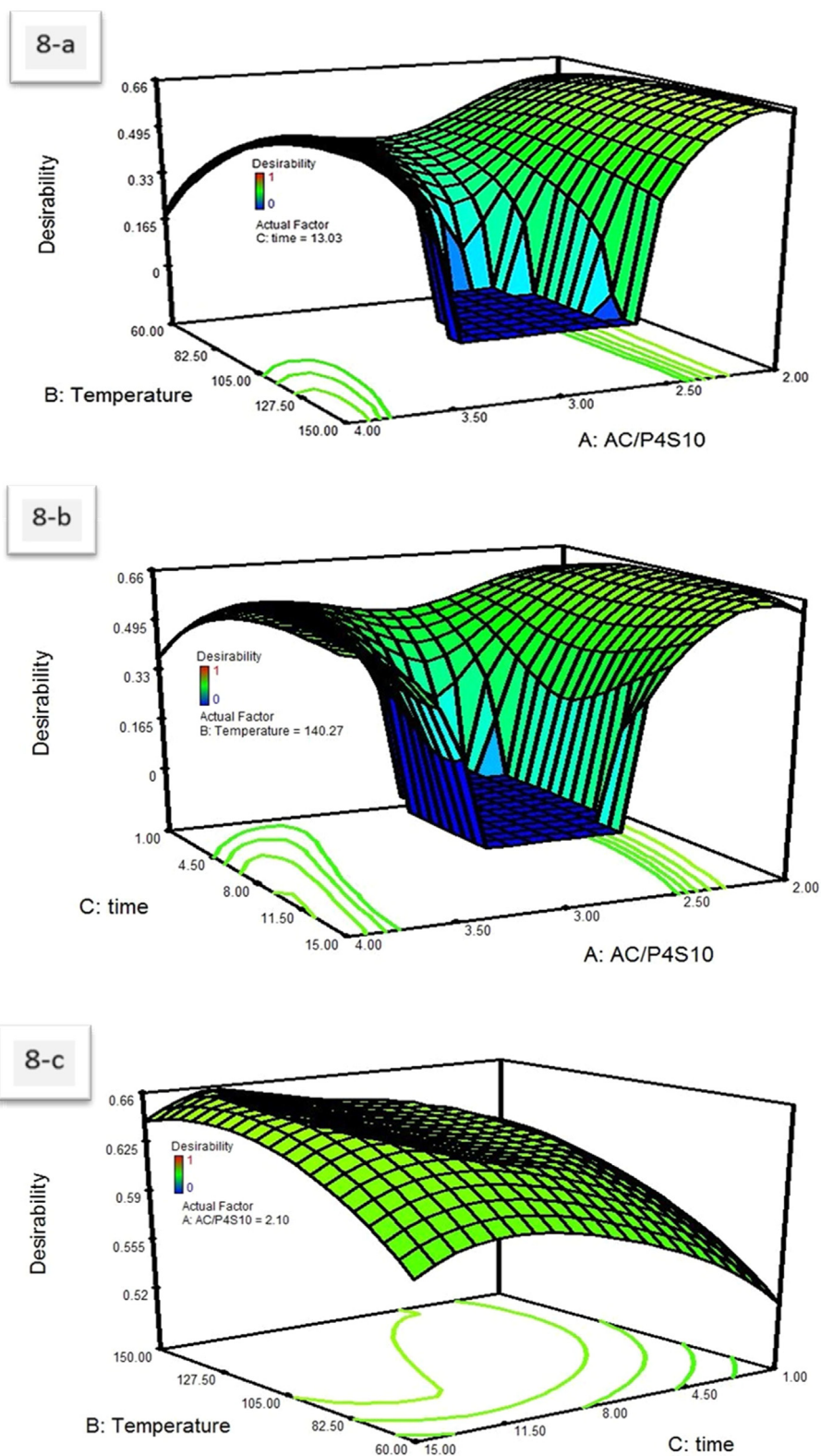


Fig. 8. Desirability of the effect of AC/P₄S₁₀ molar ratio and reaction temperature (a); AC/P₄S₁₀ molar ratio and reaction time (b); and time and temperature of reaction (c) on the yield of TA.

the entire temperature (8-a) and time ranges (8-b), while the minima are found for intermediate values of the variables.

It is interesting to note that values close to the unity are never reached for the desirability function due to the compromise between MP and MI (defined by an inverse relationship).

3.6. Validation of the model

To verify the suitability of the model, equations and optimized conditions, an experiment was carried out with the parameters suggested. Table 6 presents the results of the experiment conducted under optimal conditions, where the experimental values for yield, MI and MP

Table 6

Verification of optimum condition suggested: ratio of 2.10, time of irradiation of 14 min and a temperature 140 °C.

Response	Predicted (%)	Experimental (%)	95% CI low	95% CI high
Yield	99,37	100	96,03	102,7
MI	30,34	29	28,6	32,08
MP	3,38	3,45	3,22	3,54

were found to be 100%, 29,00 kg/Kg and 3.45%, respectively. The results of analysis indicated that the experimental values were in excellent agreement with the predicted values. In S.I. other experimental set of conditions support the validation of the design.

4. Conclusions

The response surface methodology (RSM) was used to optimize the reaction parameters for thionation of acetamide, using economical reagent and solid support (P_4S_{10}/Al_2O_3), and microwave-assisted methods. In order to evaluate the efficiency in sustainable terms, the reaction yield (ϵ), mass intensity (MI) and mass productivity (MP) were simultaneously optimized and the molar ratio AC/ P_4S_{10} , time and reaction temperature were evaluated. The derived polynomial equations were used to predict the response. We derived a quadratic regression model with satisfactory prediction. The triple optimization with the desirability function predicts a maximum yield of 100%, a 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, irradiation time of 14 min and temperature 140 °C.

Acknowledgment

This work was supported by the Consejo Nacional de Investigaciones Científicas y Tecnológicas (CONICET), FONCYT and SeCyT of the Universidad Nacional de Córdoba. R. E. Domínguez thanks CONICET for the fellowship granted.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at <http://dx.doi.org/10.1016/j.scp.2018.05.004>.

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