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Statistical Optimization of Reaction Parameters for the Synthesis of 2,4,6,8,10,12-Hexanitro-2,4,6,8,10,12-hexaazaisowurtzitane

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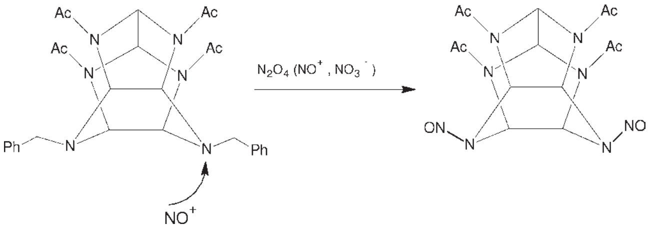
ABSTRACT: An orthogonal array design (OA_{32}) was employed as a statistical optimization method to enhance the performance of the synthesis of 2,4,6,8,10,12-hexanitro-2,4,6,8,10,12-hexaazaisowurtzitane (HNIW). The current application of the Taguchi method was successful in optimizing the experimental parameters of HNIW synthesis. High-purity HNIW was synthesized on a relativity large scale by the one-pot method using addition of N_2O_4, HNO_3, and H_2SO_4 to tetraacetyldibenzylhexaazaisowurtzitane (TADB). The effects of reaction conditions such as the TADB:N_2O_4, N_2O_4:HNO_3, and HNO_3:H_2SO_4 ratio, the temperature of nitrosation, the temperature of addition of HNO_3 and addition of H_2SO_4, the time of nitrosation, and the time of addition of HNO_3 and H_2SO_4 on the yield of synthesized HNIW were investigated. The effects of these factors on the yield of HNIW were quantitatively evaluated by the analysis of variance (ANOVA). The results showed that the yield of HNIW synthesis can be enhanced significantly by controlling the temperature of addition of H_2SO_4 and the time of nitrosation. Finally, optimal conditions for synthesis of HNIW by the one-pot method were proposed. The results of ANOVA showed that the optimal TADB:N_2O_4, N_2O_4:HNO_3, and HNO_3:H_2SO_4 ratios are 6, 1:2, and 1:1, respectively; also, the optimal temperatures for nitrosation, addition of HNO_3, and addition of H_2SO_4 are 60, 20, and 60 °C, respectively, and the optimal times for nitrosation, addition of HNO_3, and addition of H_2SO_4 are 10, 0.5, and 2.5 h, respectively, for producing HNIW. Finally, under optimal conditions, the yield of the reaction is ~96%.

1. INTRODUCTION

One of the most interesting energetic molecules developed in recent years is the polycyclic nitramine, 2,4,6,8,10,12-hexanitro-2,4,6,8,10,12-hexaazaisowurtzitane (2,4,6,8,10,12-hexanitro-2,4,6,8,10,12-hexaazatetracyclododecane, HNIW, or CL-20). Many reports of the chemical and physical characteristics of this energetic compound have been published; also, these are reviewed in a recent paper by Nielsen et al.[1] There has been much literature about the synthesis of HNIW,[2−5] and several precursors for the preparation of HNIW have been introduced.[1,2,6] Among all of the precursors, the following compounds are thought to be worthy for synthesis of HNIW: TADB (tetraacetyldibenzylhexaazaisowurtzitane), TADE (tetraacetyldiethylhexaazaiowurtzitane), TADF (tetraacetyldiformylhexaazaisowurtzitane), TAIW (tetraacetylhexaazaisowurtzitane), and HAIW (hexaacetylhexaazaisowurtzitane).[3] All of the known methods for producing HNIW are based on the same starting material, 2,4,6,8,10,12-hexabenzyl-2,4,6,8,10,12-hexaazaisowurtzitane (HBIW), which is prepared by reacting benzylamine and glyoxal in an acetonitrile solvent at 25 °C.[7,8] In the synthesis of HNIW, HBIW is first reductively acylated to form TADB. The remaining benzyl groups can then be removed either by reductive formylation, with formation of TADF, or by nitrosation, leading to tetraacetyldinitrosohexaazaisowurtzitane (TADNSO), which both are easily converted to HNIW by nitration with different nitrating systems.[9,10]

1.1. Mechanism of Debenzylation of TADB by Nitrosation. Previous studies showed that in the debenzylation reaction of TADB by N_2O_4 (Scheme 1), the effective attacking reagent is nitrosonium (NO^+).[3] A dynamic equilibrium between NO_2 and N_2O_4 is observed. Mainly nitrous acid exists in the form of N_2O_4, in nitric acid solution, which does not dissociate to NO^+ and NO_3^-. Meanwhile, in the strongly acidic solutions, such as a mixture of nitric and sulfuric acids, N_2O_4 can be used as both a nitration reagent and a nitrosation reagent. However, in diluted strongly acidic solutions, NO_2^+ disappears. This phenomenon has been confirmed by Raman spectra.[3] In the synthesis of HNIW, mainly N_2O_4 is used as a nitrosation reagent, with a higher concentration of NO^+.[3]

Scheme 1. Mechanism of Debenzylation of TADB by N_2O_4



1.2. Mechanism of Oxidation and Nitration of TADNSO. In the synthesis of HNIW from TADNSO, at the first step, the nitroso groups of TADNSO are oxidized by NO_2 (which acts as an effective attacking reagent) to form tetraacetyldinitrohexaazaisowurtzitane and then are subjected to nitration by NO_2^+ (which acts as an effective attacking reagent) to form HNIW. As shown in Scheme 2, the oxidation and nitration reactions have the following mechanism. When TADB is subjected to debenzylation to form TADNSO by nitrosation, four acetyl groups and

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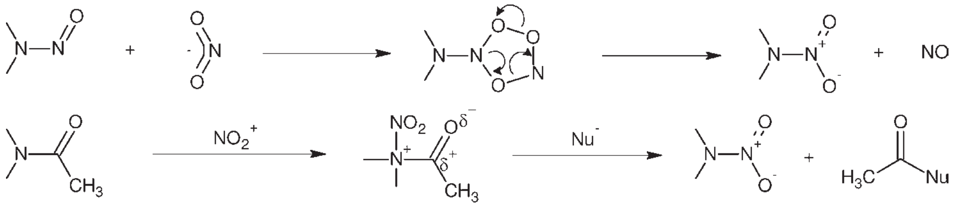
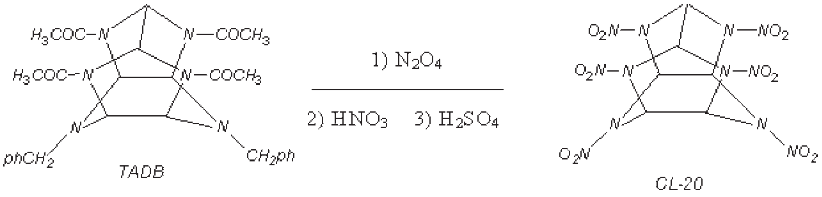
Scheme 2. Mechanism of Oxidation and Nitration of TADNSO[3]



Scheme 3. One-Pot Procedure for the Synthesis of HNIW



two nitroso groups can be easily substituted with nitro groups. Nitration of TADNSO for the preparation of HNIW is accomplished by oxidation of nitroso groups by NO_2, and nitration of acetyl groups by NO_2^+. While both nitroso and acetyl groups are easily substituted with nitro groups, the reaction can be conducted readily with appropriate nitrating reagents in short times under appropriate reaction conditions.

1.3. Optimization Strategy. Optimization is an important step in developing synthesis procedure of various materials. Two general systematic optimization procedures are simultaneous and sequential methods. In the sequential method, a small number of initial experiments is planned and conducted; succeeding experiments are based on the obtained results that may be in the direction of the increase (or decrease) of the response. In the sequential method, a maximum (or minimum) is reached. On the other hand, the simultaneous method plans a complete set of experiments (experimental design) beforehand. Then, all the experiments are conducted, and the results are used to fit a mathematical model. In the simultaneous method, a maximum (or minimum) could be found by examining the properties of the fitted model. Disadvantages of sequential methods are the slow convergence on a complex response surface and difficulty in dealing with a response surface with high dimensionality.[11−13] On the other hand, the simultaneous optimization methods do not suffer from these problems. In orthogonal array designs, orthogonal arrays are used to assign factors to a series of combinations of experiments whose results can then be analyzed by using a common mathematical procedure. The main effects of the factors and preselected interactions are independently extracted. In an orthogonal array, different combinations of numerals of any two columns have equal appearance. Via an orthogonal arrangement of experiments, different effects can be separated. However, in an orthogonal array design, by using the associated triangular table, the variables are easily assigned and quantitatively estimated. This advantage is more significant when more complicated experiments are designed.[14−18]

Taguchi statistical experimental design has been widely employed in various chemical optimization procedures, because statistical experimental design methods carefully explored the experimental space while various variables were studied using a small number of observations.[18−20] Therefore, many control factors can be simultaneously studied and optimized by statistical design. Optimization of reaction variables during the synthesis of HNIW is very important for economical manufacturing, because performing the synthesis of HNIW under optimal conditions increases the reaction yield, reduces the required time for synthesis, and makes it possible to obtain a pure product that reduces the separation and purification costs.

The objective of this work was to apply the Taguchi robust design for optimization of various parameters affecting synthesis and to evaluate the effect of these parameters on the yield of HNIW synthesis. Therefore, in this study, we used TADB as the starting material with N_2O_4 as the nitrosation agent and HNO_3 and H_2SO_4 as nitration agents for the synthesis of HNIW. Our aim in this work was the optimization of conditions to enhance the yield of the synthesis of HNIW and the reduction of the time required for the reaction.

Here, HNIW was prepared by a one-pot procedure, as shown in Scheme 3.[10] TADB was reacted with dinitrogen tetroxide at various temperatures and different reaction times to give TADNSO. Nitric acid was then added to the reaction solution at various temperatures and different reaction times. Then, sulfuric acid was added to the solution at various temperatures and different reaction times. To the best of our knowledge, various reports about the synthesis of HNIW by one or two-pot reactions could be found;[2] however, the aim of these reports was only synthesis of the HNIW without focusing on the yield of the reaction. Therefore, all of these reports suffer from two main limitations: the low purity of the product and the requirement of a long time to completion of the reaction. Hence, optimization of parameters affecting the synthesis reaction for preparation of HNIW during a short period with a high yield is of interest.

2. EXPERIMENTAL SECTION

2.1. Materials and Instrument. The starting material TADB was synthesized and purified as proposed in ref 19. N_2O_4 was used as received from Sigma-Aldrich. Also, fuming HNO_3 [100% (v/v) pure] and H_2SO_4 [98% (v/v) pure] were used as received from Merck. All synthesized HNIW samples were characterized

Table 1. Assignment of the Factors and Levels of the Experiments Using an $OA_{32}(4^9)$ Matrix and Yields of HNIW Produced as a Result

trial	TADB (g): N_2O_4 (mL) ratio	HNO_3 (mL): H_2SO_4 (mL) ratio	N_2O_4 (mL): HNO_3 (mL)	temp of nitrosation (°C)	temp of addition of HNO_3 (°C)	temp of addition of H_2SO_4 (°C)	temp of nitrosation (h)	time of addition of HNO_3 (h)	time of addition of H_2SO_4 (h)	yield (%)
1	1	2:1	2:1	0	0	0	1	0.5	0.5	0.0
2	1	1:1	1:1	20	10	30	5	1	1.5	0.0
3	1	1:2	1:2	40	20	60	10	1.5	2.5	81.3
4	1	1:3	1:3	60	30	90	15	2	3.5	5.0
5	2	2:1	2:1	20	10	60	10	2	3.5	42.0
6	2	1:1	1:1	0	0	90	15	1.5	2.5	15.5
7	2	1:2	1:2	60	30	0	1	1	1.5	40.0
8	2	1:3	1:3	40	20	30	5	0.5	0.5	21.0
9	4	2:1	1:1	40	30	0	5	1.5	3.5	0.0
10	4	1:1	2:1	60	20	30	1	2	2.5	74.0
11	4	1:2	1:3	0	10	60	15	0.5	1.5	61.3
12	4	1:3	1:2	20	0	90	10	1	0.5	81.3
13	6	2:1	1:1	60	20	60	15	1	0.5	70.0
14	6	1:1	2:1	40	30	90	10	0.5	1.5	89.7
15	6	1:2	1:3	20	0	0	5	2	2.5	0.0
16	6	1:3	1:2	0	10	30	1	1.5	3.5	23.0
17	1	2:1	1:3	0	30	30	10	1	2.5	59.5
18	1	1:1	1:2	20	20	0	15	0.5	3.5	0.0
19	1	1:2	1:1	40	10	90	1	2	0.5	68.0
20	1	1:3	2:1	60	0	60	5	1.5	1.5	60.0
21	2	2:1	1:3	20	20	90	1	1.5	1.5	62.5
22	2	1:1	1:2	0	30	60	5	2	0.5	9.0
23	2	1:2	1:1	60	0	30	10	0.5	3.5	24.0
24	2	1:3	2:1	40	10	0	15	1	2.5	0.0
25	4	2:1	1:2	40	0	30	15	2	1.5	0.0
26	4	1:1	1:3	60	10	0	10	1.5	0.5	33.3
27	4	1:2	2:1	0	20	90	5	1	3.5	3.0
28	4	1:3	1:1	20	30	60	1	0.5	2.5	35.0
29	6	2:1	1:2	60	10	90	5	0.5	2.5	87.5
30	6	1:1	1:3	40	0	60	1	1	3.5	87.5
31	6	1:2	2:1	20	30	30	15	1.5	0.5	0.0
32	6	1:3	1:1	0	20	0	10	2	1.5	13.0

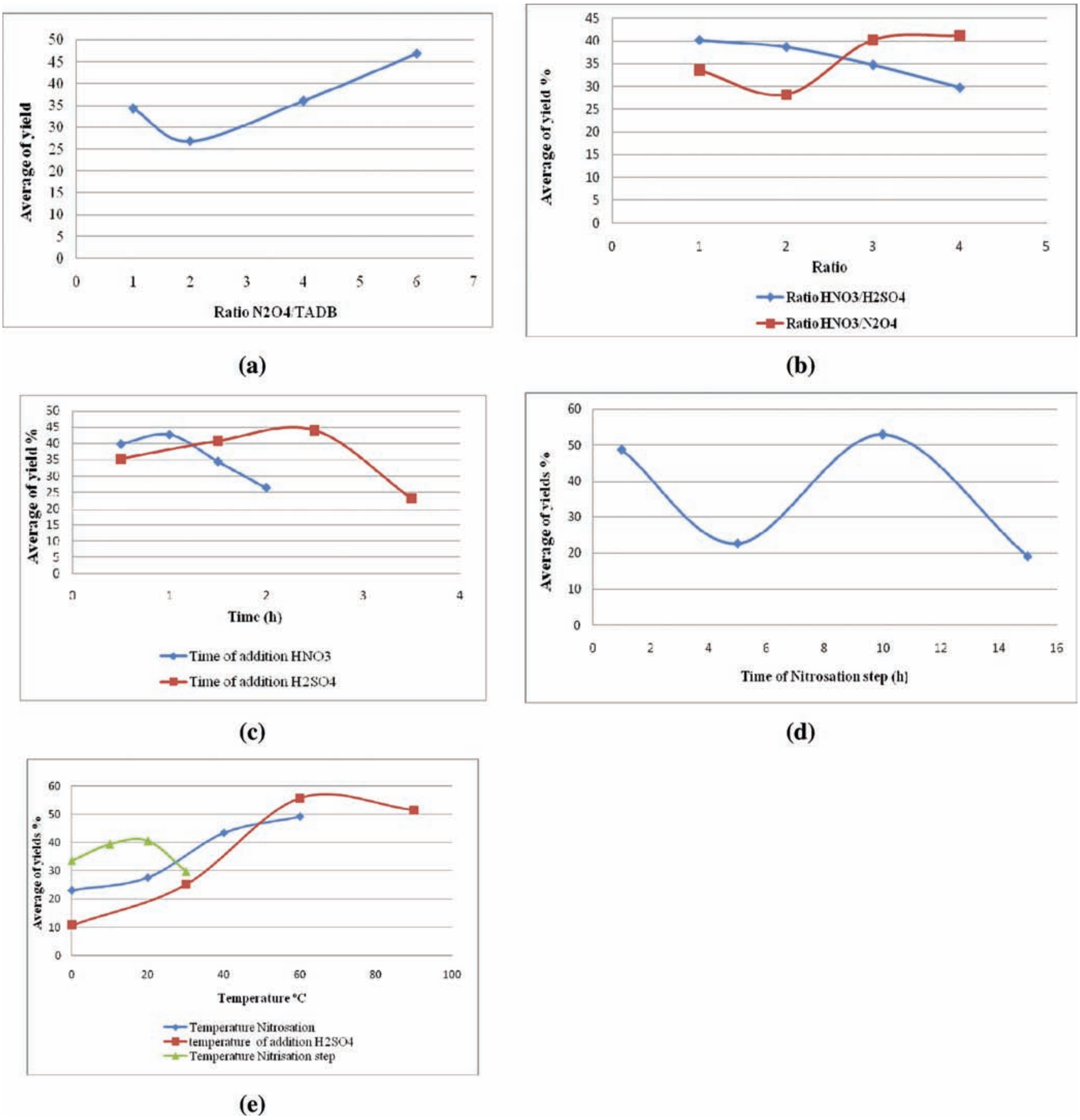
by melting point and TLC. Meanwhile, more characterization was conducted for the HNIW sample prepared under optimal conditions by ^1H NMR, FT-IR, and HPLC. IR spectra were recorded with a Perkin-Elmer infrared spectrometer using matrix KBr. ^1H NMR spectra were recorded on a Bruker 300 MHz instrument model WG-300 and δ units with reference to a tetramethylsilane internal standard. HPLC was conducted with a Waters 600 pump with a C_{18} column/UV detector.

2.2. Procedure. HNIW was prepared by adding N_2O_4 at various ratios to TADB with gentle stirring and at various temperatures. After the required times had passed, HNO_3 (at a particular temperature and a specified time) and H_2SO_4 (at a particular temperature and a specified time) were added to the former solution, alternatively. The resultant reaction mixture was quenched by being poured into an ice/water bath.

To optimize experimental reaction parameters for the synthesis of HNIW, an experimental design approach (OA_{32}) was followed. The variables (TADB:N_2O_4, N_2O_4:HNO_3, and HNO_3:H_2SO_4 ratios, temperature of nitrosation, temperatures of addition of HNO_3 and H_2SO_4, time of nitrosation, and times of addition of HNO_3 and H_2SO_4) are listed in Table 1.

3. RESULTS AND DISCUSSION

In simultaneous optimization methods, such as mixture designs and factorial designs, the experiments to be conducted have been previously described.[18,20,21] The experimental results are collected, and then the optimum condition can be located by constructing a response surface or by retention mapping. One obvious disadvantage of the full factorial designs is that the number of experimental trials required increases geometrically with an increasing number of variables. Thus, the number of experimental trials expands so rapidly that it is not feasible to implement these trials. Fortunately, this can be minimized by the use of fractional factorial experiments, such as orthogonal array (OA) designs. The latter methods have an advantage over the former in that three-level designs can be used, to extract information more precise than that obtained from the two-level



(a) (b) (c) (d) (e)

Figure 1. Average yields of HNIW synthesis corresponding to each level of various factors: (a) N_2O_4:TADB ratio, (b) H_2SO_4:HNO_4 and HNO_3:N_2O_4 ratios, (c) time of addition of HNO_3 and H_2SO_4, (d) time of nitrosation, and (e) temperatures of nitrosation, addition of H_2SO_4, and addition of HNO_3.

designs. In orthogonal array designs, orthogonal arrays are used to assign factors to a series of combinations of experiments whose results can then be analyzed by using a common mathematical procedure. The main effects of the factors and preselected interactions are independently extracted. In an orthogonal array, different combinations of numerals of any two columns have equal appearance. Via an orthogonal arrangement of experiments, different effects can be separated.[22−24]

3.1. Optimization of Reaction Parameters for the Synthesis of HNIW. In this work, HNIW was prepared by a one-pot procedure, similar to that reported in ref 10. TADB was reacted with dinitrogen tetroxide at different temperatures for various times (in accordance with Table 1) to give TADNSO. Then, nitric acid and sulfuric acid, successively, were added to the solution. The resulted reaction mixture was quenched by pouring it into an ice/water bath. The purpose of this study was to determine how the various reaction parameters affect the yield of HNIW synthesis reaction. The factors included in this study were temperatures and times that correspond to the reaction of dinitrogen tetroxide, in addition to the times for addition of nitric acid and sulfuric acid.

Table 2. ANOVA Results for Optimization of HNIW Synthesis with the $OA_{32}(4^9)$ Matrix

					pooled[a]			
factor	code	DOF	S	V	DOF	S′	F′	P′
TADB (g):N_2O_4 (mL) ratio	C[N_2O_4]	3	1563.6	521.2	–	–	–	0
HNO_3 (mL):H_2SO_4 (mL) ratio	R[AN/AS]	3	516.7	172.2	–	–	–	0
N_2O_4 (mL):HNO_3 (mL) ratio	R[N_2O_4/AN]	3	900.8	300.3	–	–	–	0
temp of nitrosation (°C)	T1[NO]	3	3749.4	1249.8	3	3749.4	2.53	6.9
temp of addition of HNO_3 (°C)	T2[AN]	3	618.6	206.2	–	–	–	0
temp of addition of H_2SO_4 (°C)	T3[AS]	3	11081.6	3693.9	3	11081.6	7.48	29.0
time of nitrosation (h)	t1[NO]	3	7378.2	2459.4	3	7378.2	4.98	17.8
time of addition of HNO_3 (h)	t2[AN]	3	1230.8	410.3	–	–	–	0
time of addition of H_2SO_4 (h)	t3[AS]	3	2051.9	684.0	–	–	–	0
error	E	4	3989	997	22	10871.2	–	46.3

[a] The critical value was at a 90% confidence level; the pooled error results from pooling insignificant effects.

Factors and levels tested are reported in Table 1. Also, the yield of the synthesis in each experiment is given in this table as a response. In this study, the investigated variables were independent and have no considerable interaction, because times, temperatures, and ratios corresponded to the separated steps of the synthesis.

The analysis of data while there is no interaction between variables includes (1) determination of the optimal conditions, (2) identification of the individual influence of each factor on the result that in this study is the yield of the synthesis, and (3) estimation of the yield under optimal conditions.

The mean values that correspond to the effect of the factors at each level were calculated according to assignment of the experiment. In fact, computing the yield of the synthesis corresponds to, for example, the effect of time of addition of nitric acid at level 1 (0.5 h) conducted by pooling the yield of the synthesis among all the trials in which time for addition of nitric acid was set at level 1 (trials 1, 8, 11, 14, 18, 23, 28, and 29) and dividing by the number of trials at this level (here 8). Figure 1 shows the average yield of HNIW synthesis for each level of any factor. As shown by the curves in Figure 1, the average yield for each factor will change when the level of the factor is varied.

Table 2 shows the data obtained by analysis of variance (ANOVA), which was conducted with the results of the experiments (yields of synthesis). In this study, the effects of the TADB:N_2O_4, HNO_3:H_2SO_4, and N_2O_4:HNO_3 ratios on the yield of HNIW synthesis at four different levels were investigated. It was found that these ratios are not significant parameters for controlling the yield of HNIW synthesis. Also, the effect of the temperature of various steps such as nitrosation, addition of acid nitric, and addition of sulfuric acid on the yield of HNIW synthesis was studied. Four different temperatures for each step were investigated. Our finding showed that temperatures of nitrosation and addition of sulfuric acid are significant parameters in controlling the yield of the synthesis. Another investigated parameter for controlling the yield of HNIW synthesis was the time of various steps. Four different times were investigated for nitrosation, addition of nitric acid, and addition of sulfuric acid. The results of ANOVA showed that only the time of nitrosation is a significant parameter for the controlling the yield of HNIW synthesis and the time of addition of nitric acid and addition of sulfuric acid is not significant for controlling the yield of HNIW synthesis.

The results of ANOVA for these experiments indicate that (at a 90% confidence level) only the temperature of nitrosation and the temperature of addition of sulfuric acid have significant effects on the yield of the synthesis reaction and all other variables have no significant effects on the yield of HNIW synthesis. In this work, there was no considerable interaction between the variables. The results of ANOVA indicated that a temperature of 60 °C for the nitrosation step is optimal for the synthesis of HNIW. Also, with an increase in the temperature of addition of sulfuric acid from 30 to 60 °C, the yield of the synthesis was increased. However, at a higher temperature of 90 °C, the yield of the reaction decreased. Therefore, 60 °C was selected as the optimal temperature for addition of sulfuric acid during HNIW synthesis. Also, among various tested times, 10 h for nitrosation was the optimal time for this step. Under the optimized conditions, obtained from the OA_{32} matrix (Table 2), the performance of the procedure (yield of HNIW synthesis) could be predicted according to the following expression:[14,15]

$$Y_{opt} = \frac{T}{N} + \left(T_{NO} - \frac{T}{N}\right) + \left(T_{H_2SO_4} - \frac{T}{N}\right) + \left(t_{NO} - \frac{T}{N}\right)$$

where T/N is the average yield of the synthesis reaction plus the contribution of T_{NO}, $C_{H_2SO_4}$, and t_{NO} above average performance; T is the grand total of yields for all runs; N is the total number of results; Y_{opt} is the yield of the synthesis under optimal conditions; and T_{NO}, $C_{H_2SO_4}$ and t_{NO} are average yields of the synthesis at optimal levels of temperature for nitrosation, temperature of sulfuric acid addition, and time for nitrosation, respectively. On the other hand, under the optimal conditions, the confidence interval (CI) for the yield of the synthesis is calculated using the following expression:[14]

$$CI = \pm\sqrt{\frac{F_\alpha(f_1, f_2)V_e}{N_e}}$$

where $F_\alpha(f_1,f_2)$ is the F value from the F table at degrees of freedom (DOF) f_1 and f_2 at level of significance α (in this work, $\alpha = 90\%$), f_1 is the DOF of the mean (which always equals 1), f_2 is the DOF of the pooled error term, and N_e is the effective number of replications, given by N_e = (number of trials)/[DOF of the mean (always equals 1) + total DOF of factors used for the prediction]. Calculations for the prediction of the yield of HNIW synthesis under optimal conditions and CI for this estimated yield of reaction showed that at a 90% confidence level under optimal conditions, the yield of HNIW synthesis will be approximately 87 ± 15%.

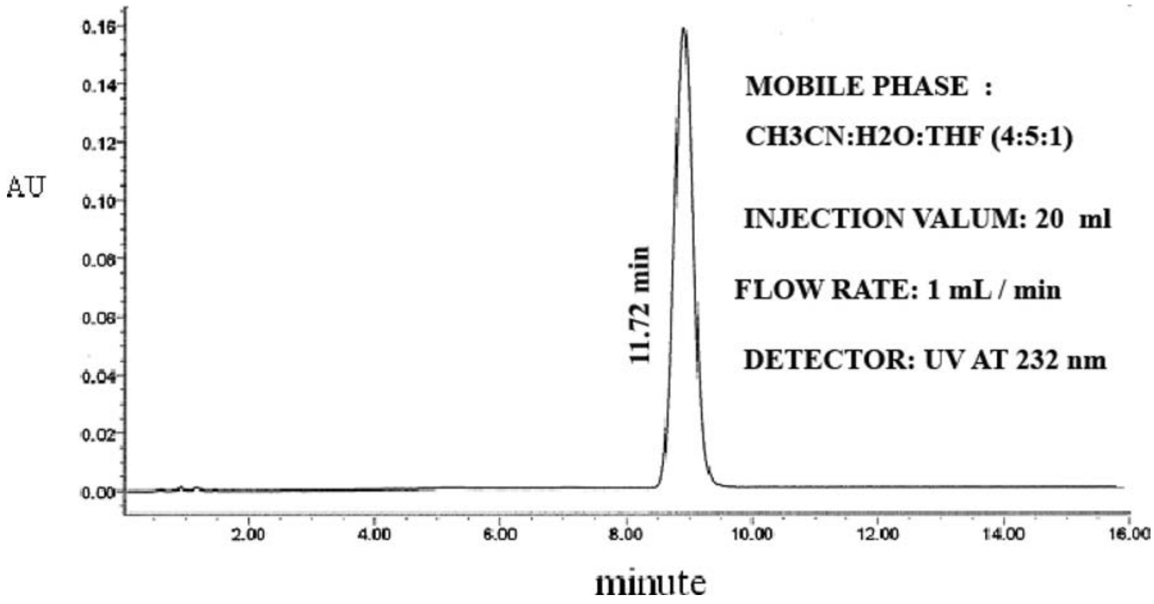


Figure 2. HPLC chromatogram of synthesized HNIW under optimal conditions.

3.2. Characterization of Synthesized HNIW under Optimal Conditions. In the next step of this investigation, HNIW was prepared under optimal conditions obtained from the results of ANOVA (60 °C temperature for nitrosation, 60 °C temperature for sulfuric acid addition, and 10 h time for nitrosation). The yield of the reaction was ∼96%. Meanwhile, the results of TLC revealed that the prepared HNIW under optimal conditions was absolutely pure. The prepared HNIW sample under optimized conditions of synthesis was used for HNMR, FT-IR, and HPLC studies. The melting point (239 °C) and FTIR and H NMR spectra were identical to those reported previously.[2,10,25−28] The HPLC chromatogram of the prepared HNIW sample under optimal conditions is presented in Figure 2. As one could see from this chromatogram, the synthesized HNIW under optimal conditions is highly pure and no peak that corresponds to the impurity was observed.

4. CONCLUSION

HNIW was synthesized by the one-pot method described in this work. The Taguchi robust design method was used to optimize the reaction parameters of HNIW synthesis for obtaining the product with high yield over a relatively short period of time. Various factors affecting the yield of the synthesis were analyzed and optimized. As a result, the temperature of nitrosation, the temperature of addition of sulfuric acid, and the time required for nitrosation have significant effects on the yield of HNIW synthesis. Under optimal conditions for synthesis, HNIW in an ∼96% yield with absolute purity could be prepared.

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