



Statistical Optimization of a Novel Approach for the Reductive Debenzylation of 2,4,6,8,10,12-Hexabenzyl-2,4,6,8,10,12-hexaazaisowurtzitane Using Pd@SiO₂ Nano Catalyst

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Abstract: The synthesis of 2,6,8,12-tetraacetyl-4,10-dibenzyl-2,4,6,8,10,12-hexaazaisowurtzitane (TADB), from 2,4,6,8,10,12-hexabenzyl-2,4,6,8,10,12-hexaazaisowurtzitane (HBIW) is a key step in the preparation of 2,4,6,8,10,12-hexanitro-2,4,6,8,10,12-hexaazaisowurtzitane (HNIW or CL-20). In this study, a novel highly efficient nano catalyst based on Pd@SiO₂ was used for the reductive debenzoylation of HBIW. It is notable that an orthogonal array design OA₉ was applied as a statistical optimization method for the synthesis of TADB. The current application of the Taguchi method in optimizing the experimental parameters of the TADB synthetic procedure was successful. TADB was synthesized by investigating the effect of the reaction conditions, such as catalyst percentage, time (h) and temperature (°C). The effects of these factors on the yield of TADB were evaluated quantitatively by the analysis of variance (ANOVA). The Pd@SiO₂ nano catalyst, consisting of a palladium core with SiO₂ monolayer shells, was synthesized and characterized by SEM, TEM and IR spectroscopy. The optimum condition indicated that the use of fresh Pd@SiO₂ nano catalyst provides a high yield (90%). The use of Pd@SiO₂ nano catalyst after recovery gave a yield of 65%.

Keywords: Pd@SiO₂, reductive debenzoylation, nano, catalyst, Taguchi

1 Introduction

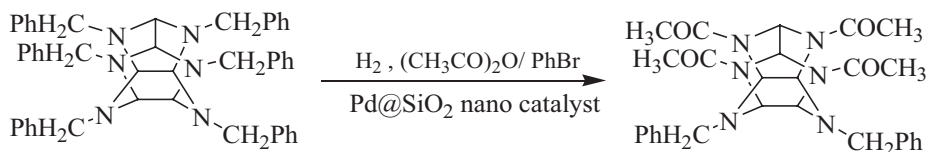
Palladium-based heterogeneous catalysts are one of the most interesting groups of catalysts due to their ability to catalyze a variety of important chemical reactions and the advantages of easy recovery and regeneration [1-6]. A critical aspect in an investigation of heterogeneous catalysis is multifunctionality in various reactions. The architectural design of a catalyst is aimed at increasing its activity and selectivity. One of the promising properties is porosity in the support material, to act as a molecular transport pathway to the active catalyst surface and to improve the total reaction rate and product selectivity. In order to prepare heterogeneous catalysts with metallic nanoparticles, including Pd, or to prevent nanoparticles from coalescing, various types of inorganic shells, such as silica [7-9], carbon and metal oxides around the nanoparticles, may be used [10-13].

2,4,6,8,10,12-Hexanitro-2,4,6,8,10,12-hexaazaisowurtzitane (HNIW, CL-20) was first synthesized by Nielsen in 1987 [14]. All known methods of producing CL-20 are based on the same starting material, 2,4,6,8,10,12-hexabenzyl-2,4,6,8,10,12-hexaazaisowurtzitane (HBIW), which is first reductively acylated to form 2,6,8,12-tetraacetyl-4,10-dibenzyl-2,4,6,8,10,12-hexaazaisowurtzitane (TADB). The remaining benzyl groups can then be removed by reductive or oxidative methods. The synthesis of HNIW from 2,6,8,12-tetraacetylhexaazaisowurtzitane (TAIW) is a favorable method, both in terms of economy and product purity. Cerium ammonium nitrate (CAN) has been reported as an oxidizing reagent for the oxidative debenylation of TADB [15]. The reported methods for the reductive debenylation of HBIW and TADB are very expensive and are limited to the application of catalysts such as palladium hydroxide on activated carbon (Pearlman's catalyst) [15, 16].

One of the well-known methods for the optimization of the reaction conditions is experimental design. The Taguchi method is a technique developed for experimental design. It is a powerful tool in the design of experiments because it can provide a simple, efficient, and systematic approach for optimizing the performance, quality, and cost [17-22]. It is notable that the Taguchi method can determine and separate the effects of different parameters with the aid of data obtained *via* performing experiments according to a proposed orthogonal array [23-25]. Therefore, many academic research groups have used Taguchi as a robust method for statistical optimization [26-28].

In the continuation of our study of the synthesis of HNIW and its precursors [29, 30], the application of statistical optimization and a consideration of all of the problems encountered with previous procedures for the reductive debenylation of HBIW, such as low yield and high cost, our previous experience and the fact

that Pd@SiO₂ can catalyze debenzoylation, it was decided to explore the use of the latter catalyst for the reductive debenzoylation of HBIW (Scheme 1).



Scheme 1. Reductive debenzoylation of HBIW with Pd@SiO₂ nano catalyst

2 Experimental

2.1 Chemicals and materials

Commercially available solvents and reagents as supplied by Merck were used without further purification. HBIW was prepared according to a published procedure [29]. Melting points were determined in an open capillary. IR spectra were recorded on a Perkin-Elmer infrared spectrometer using a KBr matrix. ¹H NMR was recorded on a Bruker 300 MHz instrument model WG-300 and δ values were referred to tetramethylsilane as an internal standard. Scanning electron microscopy (SEM) was utilized to evaluate the surface topology of the catalyst. SEM images were obtained on a Hitachi S4160 instrument.

2.2 Pd@SiO₂ nano catalyst preparation

For the preparation of Pd@SiO₂ nano catalyst, the first step involved the preparation of SiO₂ spheres by mixing ethanol (43.7 mL, 0.75 mol), water (5.6 mL), tetraethylorthosilicate (2.23 mL, 0.01 mol) and aqueous ammonia (9.3 mL, 0.04 mol) in a 250 mL beaker and stirring magnetically for 30 min at room temperature. The formation of a cream suspension indicated the termination of the first step. In the second step, for the preparation of the Pd@SiO₂ nano catalyst, a solution of Na₂PdCl₄ (0.1 g PdCl₂ in 20 mL 20% NaOH) was added dropwise to the cream suspension and stirred magnetically for 3 h at room temperature. Finally, the precipitated cream Pd@SiO₂ nano catalyst was filtered off and dried overnight in an oven at 50 °C.

2.3 Optimized procedure for the synthesis of TADB

The catalytic debenzoylation of HBIW was carried out in a pressure reactor with a mixture of HBIW (6 g, 8.5 mmol) in dimethylformamide (DMF; 60 mL) and freshly prepared Pd@SiO₂ catalyst (0.25 g, 0.1-0.3 wt.%, of total Pd@SiO₂

relative to the HBIW). In order to provide a source of hydrogen bromide, bromobenzene (0.45 mL, 4.28 mmol) was added to the reaction mixture as a co-catalyst. The hydrogenolysis of the C–N bond can be accelerated in the presence of C_6H_5Br . Thereafter, acetic anhydride (Ac_2O ; 9 mL, 95.5 mmol) as the acetylating agent was added to the mixture. During the reaction, the hydrogen pressure and reaction temperature were maintained at 4 atm and 40 °C, respectively. The hydrogenolysis was performed over a 4 h period. At the end of the experiment, the catalyst and the product TADB were filtered off (sinter porosity 4). The precipitated TADB was dissolved in a mixture of chloroform (20 mL) and acetic acid (30 mL), and the remaining $Pd@SiO_2$ catalyst was filtered off. Water (50 mL) was added to the solution of TADB in chloroform/acetic acid, the TADB was precipitated, and was filtered off.

3 Results and Discussion

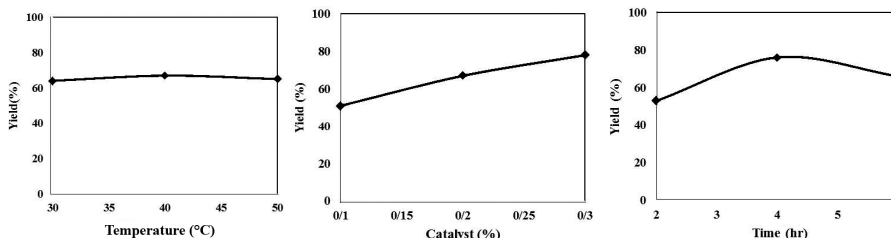
3.1 Optimization of the reaction parameters for the synthesis of TADB by experimental design

In order to choose suitable operation conditions for the synthesis of TADB by the reductive debenylation of HBIW, the experimental design approach was adopted. Initially, in order to identify the factors and levels for the experimental design, some preliminary experiments were performed. As shown in Table 1, three experimental parameters of the reaction, namely catalyst per cent, time (h) and temperature (°C), were studied at three different levels by the L9 orthogonal array proposed by the Taguchi robust design. The investigated parameters and levels in each experiment are shown in Table 1. The upper and lower levels for all of the factors investigated and just logical ranges chosen for the experimental design. The last column of Table 1, gives the yield of the reaction under the operational conditions of each experiment.

The Taguchi Statistical Optimization consists of three steps as follows: (1) identification of the optimal operation conditions of the reaction; (2) evaluation of the individual effects of any studied variable in the response, which in the present study was the yield of the reaction; and (3) determination of the response to the process under the identified optimum conditions. Figure 1 presents the curves obtained, corresponding to the effect of each parameter on the yield of the reaction. The graphs of Figure 1 show the variations in reaction yield caused by the level changes in the investigated variables.

Table 1. Assignment of the factors and levels of the experiments using an OA9 (3^3) matrix and yield of reaction as the response

Entry	Time [h]	Catalyst (Pd@SiO ₂) [%]	Temperature [°C]	Yield [%]
1	2	0.1	30	40
2	2	0.2	40	55
3	2	0.3	50	65
4	4	0.1	40	62
5	4	0.2	50	80
6	4	0.3	30	87
7	6	0.1	50	50
8	6	0.2	30	60
9	6	0.3	40	83

**Figure 1.** Effects of level variation for the studied parameters on the synthesis of TADB: (a) Temperature, °C; (b) Catalyst % (Pd@SiO₂ wt.%, of total Pd@SiO₂ relative to the HBIW); (c) Time, h

Analysis of variance (ANOVA) was performed for the experimental data obtained (reaction yield of TADB synthesis by the reductive debenylation of HBIW). Table 2 presents the ANOVA results for the effects of the investigated parameters. As may be seen from this table, at a confidence level of 90%, except for temperature, the other variables, reaction time and catalyst percentage, have significant effects upon the yield of the reaction.

The ANOVA analysis indicated that the reaction temperature has no significant effect at the investigated levels for controlling the yield of the reaction. However, the catalyst per cent has the most important effect on the yield, and of the studied levels (0.1%, 0.2% and 0.3%), 0.3% showed the best efficiency. For the other studied parameter, time, the best level for this factor was 4 h.

Table 2. ANOVA results for procedure optimization for the synthesis of TADB by OA₉ (3³) matrix

Factor	DOF ^a	S ^a	V ^a	p ^a
Time [h]	2	796.2	398.1	38.6
Catalyst [%]	2	1157.5	578.7	56.8
Temperature [°C]	2	10.9	5.4	0
Error	2	26.9	13.4	4.6

^a DOF: degree of freedom; S: standard deviation;
V: variance; p: participation of each factor in the result

As proposed by ANOVA and considering the average effect of each parameter (Figure 3), the optimum conditions for the synthesis of TADB are: temperature 40 °C, catalyst 0.3% and time 4 h. The yield of TADB may be estimated using the following expression [33]:

$$Y_{opt} = \frac{T}{N} + \left(P - \frac{T}{N} \right) + \left(F_{sol} - \frac{T}{N} \right) + \left(S_{Nature} + \frac{T}{N} \right) + \left(SUR_{type} - \frac{T}{N} \right) \quad (1)$$

where T/N is the average yield of the reaction for all 9 experiments + contributions of F_{sol} , S_{Nature} and SUR_{type} , for the level which produced the maximum yield calculated from the average effect of each factor (Figure 3); T is the overall value of the reaction yield in all runs of Table 1, N is total number of experiments, Y_{opt} is the yield under optimum conditions, P , F_{sol} , S_{Nature} and SUR_{type} are the calculated average yield of the reaction at the optimum levels of time, catalyst per cent and temperature, respectively. The results of the estimation of the reaction yield for the reductive synthesis of TADB, at 90% confidence level, indicate that the reaction yield under the optimum conditions will have an average of 91%. In the next stage of this work, TADB was synthesized under the optimum conditions suggested by ANOVA. The average yield of TADB obtained under these optimum conditions was about 90%.

3.1.1 Catalyst characterization

An SEM image of the Pd@SiO₂ nano catalyst is shown in Figure 2. As may be seen in Figure 2, the Pd@SiO₂ nano catalyst particles are spherical and uniform. The average size of the Pd@SiO₂ nano catalyst was measured as having a mean diameter of 50 nm to 75 nm. A Transmission electron microscopy image of Pd@SiO₂ nano catalyst is shown in Figure 3. The TEM image confirms that the catalyst particles have an average of less than 100 nm.

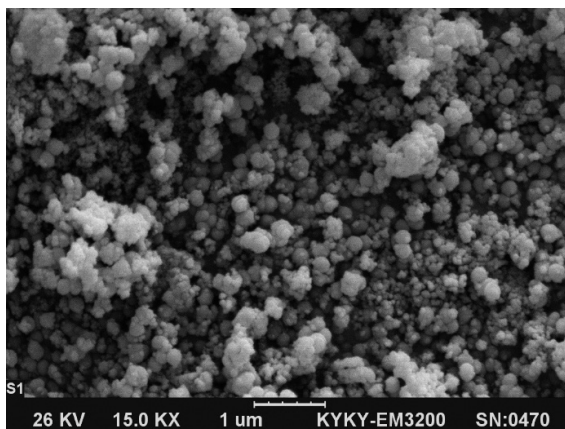


Figure 2. SEM image of Pd@SiO₂ nano catalyst

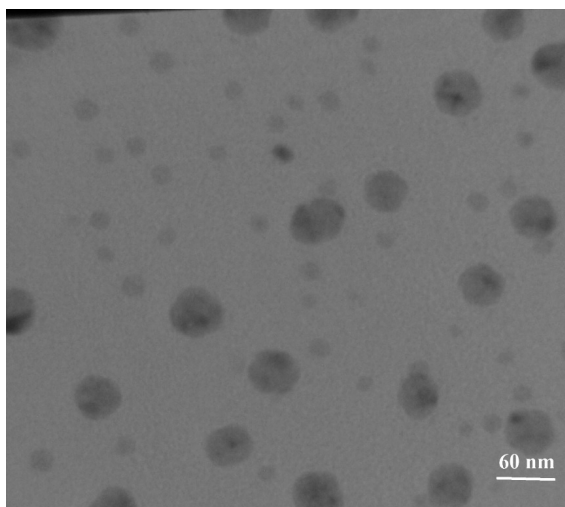


Figure 3. TEM image of Pd@SiO₂ nano catalyst

In order to investigate the final SiO₂ core cell, FT-IR analysis was performed on the Pd@SiO₂ nano catalyst. The FT-IR spectrum of Pd@SiO₂ nano catalyst is shown in Figure 4; it exhibits peaks at: 434 cm⁻¹, 819 cm⁻¹, 1250 cm⁻¹, 3500 cm⁻¹. The 434 cm⁻¹ peak was assigned to Si–O–Si out-of-plane bending, the 819 cm⁻¹ peak to Si–O–Si symmetric stretching vibrations, the 1250 cm⁻¹ peak is related to Si–O–C, and the 3500 cm⁻¹ peak is related to OH: Si–OH. These are in agreement with literature values [31].

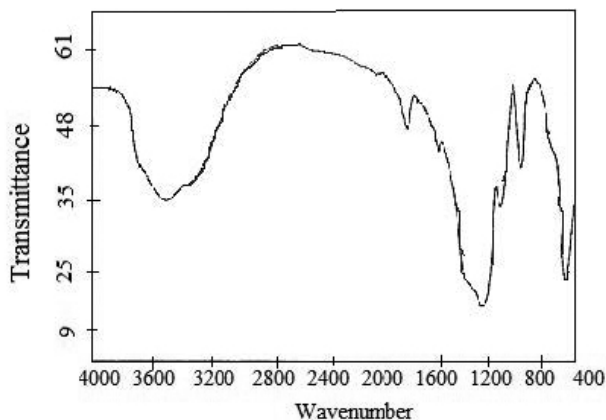


Figure 4. FT-IR spectrum of Pd@SiO₂ nano catalyst

3.1.2 Characterization of the synthesized TADB

TADB is one of most significant precursor for the synthesis of HNIW. A facile and economic method for the preparation of TADB is limited. In this study, using a novel application of the Pd@SiO₂ nano catalyst, one obstacle to the synthesis of HNIW was removed. The reaction yield was about 90%. TLC analysis (ethyl acetate : n-hexane 2:8) revealed that the TADB prepared under these experimental conditions was absolutely pure. The TADB sample prepared under these experimental conditions was used for ¹H NMR and FT-IR analysis. The ¹H NMR and FT-IR spectra of TADB are presented in Figures 5 and 6 respectively. ¹H NMR (400 MHz, DMSO, δ): 1.87-2.11 (s, 12H), 4-4.32 (s, 4H), 5.11-5.74 (d, 4H). 6.58 (d, 2H), 7.34-7.44 (m, 10H). FT-IR (KBr, cm⁻¹): 3050-3150 (s), 2000-1667(vs), 1640-1670 (vs), 1475(vs), 1465(s), 1000~1350 (w), 690~900 (w).

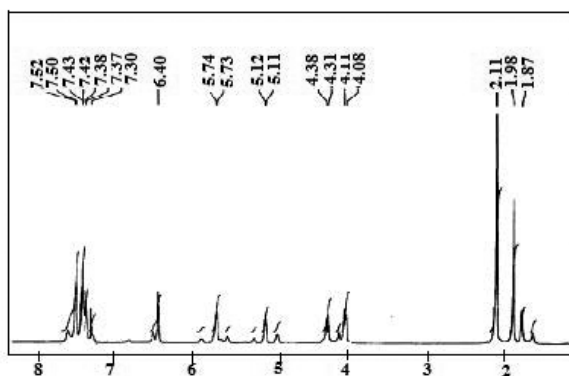


Figure 5. ¹H NMR spectrum of TADB

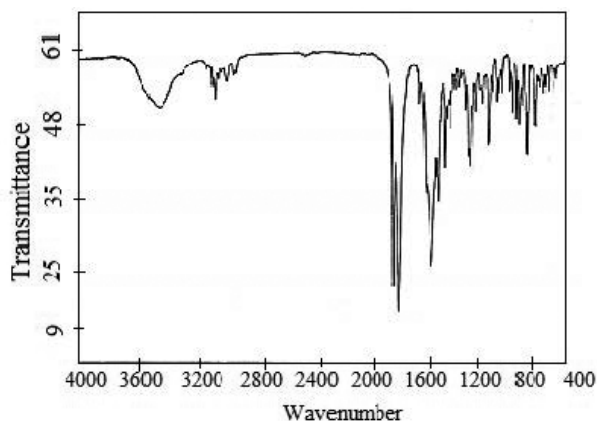


Figure 6. FT-IR spectrum of TADB

3.2 Catalyst performance in a second cycle

One of the most important deficiencies of catalysts used for the reductive debenylation of HBIW is the failure of their catalytic activity after first use under the reaction conditions. The Pd@SiO₂ nano catalyst retains its catalytic performance in a second cycle. The application of Pd@SiO₂ nano catalyst after recovery gave a yield of 65% on re-use.

4 Conclusions

In summary, a new nano catalyst Pd@SiO₂ was developed for the reductive debenylation of HBIW with good yield. Pd@SiO₂ nano catalyst is an efficient, easily prepared, sustainable and environmentally friendly catalyst for the debenylation of HBIW to TADB. The Taguchi robust design method was used to optimize the reaction parameters of TADB synthesis for obtaining the product in high yield during a relatively short reaction period. Various factors affecting the yield of the synthesis were analyzed and optimized. As a result, catalyst per cent and time required for the reaction had significant effects on the yield of TABD. Under optimal conditions of the reaction, TADB could be prepared in about 90% yield and absolute purity. One advantage of the Pd@SiO₂ nano catalyst application is its capacity for re-use; the results of the reductive debenylation demonstrated that the application of Pd@SiO₂ nano catalyst after recovery gave a yield of 65%.

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