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Solid - Solid Syntheses of Bisindolylmethane in Reciprocating Reactor

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Abstract: 3,3'-Bis-indolyl-(3-nitrophenyl)methane and 3,3'-Bis-indolyl-(4-chlorophenyl)methane were synthesized in reactor condition in this study. The impact of various factors on the yield including: time, frequency, ball and number of balls, were investigated. Investigations showed that frequency was the most effective in the useful production. Four two-millimeter balls at different stages and one, two, three and four balls were used in sequence. Yield increased by increasing number of ball to three, but with the addition of the fourth ball efficiency decreased. In general, it was observed that at the same time, frequency and number of balls, the yield of reaction between indole and 3-nitrobenzaldehyde was more than indole and 4-cholorobenzaldehyde. At a frequency of 8 Hz, 8 minutes and 3 balls, the reaction yield of indole and 3-nitrobenzaldehyde was about 72% and the reaction yield of indole and 4-cholorobenzaldehyde was about 70%. The resulting product was pink that corresponded with the references. The melting point for 3,3'-Bis-indolyl-(3-nitrophenyl)methane was measured 220°C that it has been reported in the literature in the range of 219-221°C. Indole and 4-cholorobenzaldehyde reaction product melting point was measured about 70°C that the reported amount for 3,3'-Bis-indolyl- (4-chloro phenyl) methane in the literature is about 76-77°C.

Keywords: Frequency, Ball, Indole, 4-chloro-benzaldehyde, 3-nitro-benzaldehyde, Bisindolylmethane

1. Introduction

Nowadays, many researches are conducted to offer an appropriate approach to carry out chemical processes to reach a higher output through appropriate presented methods in a shorter period without using dangerous organic solvents. Using optimal production methods, which cause the least pollution, is the best way of preventing such harmful solvents enter the environment. A solid-solid reaction without the presence of solvent is an example of this approach. Today the perspective of a cautious approach to environmental friendliness is the use of safe and environmentally friendly reactions. Indole derivatives are abundantly distributed in nature and they provide a basic framework for a number of structures and functional units in plants and animals. They are also in many compounds that show their biological and pharmacological activity [1, 2].

Indoles and their derivatives are one of the important classes of heterocyclic compounds and they are known to possess a wide range of biological activities including antioxidant, antibacterial, antiviral, antipyretic, anti-fungal, anti-inflammatory, anti-convulsant, cardiovascular [3], antimetastatic, radical scavenging, analgesic and insecticidal activity [4]. Among the various substituted indoles, bisindolylmethane derivatives (BIMs) are found which are widely distributed in the bioactive metabolites of terrestrial and marine natural sources, viz. parasitic bacteria, tunicates, and sponges [5]. BIMs are useful in the treatment of fibromyalgia, chronic fatigue and irritable bowel syndrome, and as dietary supplements for promoting healthy estrogen metabolism in humans. In addition, these compounds have potentially beneficial effects on preventing human prostate, breast, pancreatic, bladder, renal cell, lung and colon cancer and other tumor growth [6]. Moreover, these compounds may normalize abnormal cell growth associated with cervical dysplasia [1, 2, 5, 7-12].

Indole derivatives are important intermediates in organic synthesis in terms of its pharmaceutical activities, bisindolylmethane derivatives affect the central nervous system and they are used as a sedative. They have potential uses of biological activities including antibacterial, anti-microbial and anti-sugar properties [13, 14, 15].

There is a continuous demand to artificial methods of production, according to the strong biological and pharmaceutical properties of natural and synthetic derivatives of indole. Medicinal chemists use indole based compounds for the development of treatment methods and therefore different methods of synthesis are presented. In addition, oxidized forms of BIMs are utilized as dyes as well as colorimetric chemosensors [3, 4, 7, 16].

Indole derivatives and their synthesis are an important class of heterocyclic compounds in the pharmaceutical industry. An extensive reaction conditions are provided for the synthesis of bisindolylmethane derivatives in solution, in solid phase and under solvent free conditions. Protic acids as well as Lewis acids are known to promote these reactions. However, many Lewis acids are deactivated or sometimes decomposed by nitrogen-containing reactants [4]. Even when the desired reactions proceed, more than stoichiometric amounts of Lewis acids are required because the acids are trapped by nitrogen. In some cases, the reaction rate is so low that it takes a lot of time. These are the problems of different catalysts that it has been trying to resolve them in the literature [2, 13, 17].

Acid catalysts are widely used in the chemical industries; the most common of these acids are H_3PO_4, $HClO_4$ and H_2SO_4. In today's research it is tried to set toxic liquid and pollutant catalysts aside, and replacing it with solid and reusable heterogeneous catalysts. Solid acids have many advantages, including: the ease of separation of product, catalyst recovery, ease of use and reduction of the reactor and environmentally friendly disposal. Moreover, the most important challenge of heterogeneous catalysts, the control of environmental pollution, with a rigid legislation on the release of waste and toxic substances in the environment, are associated with serious implications for the chemical industry. In addition, there are a great deal of interest for the development of heterogeneous systems because of their importance in industry and technology development [13, 18].

Also solid acid catalysts based on carbon have many advantages: they are poorly soluble in common organic solvents, they have the poorly corrosive effect and they are environmentally friendly. As well as the product is easily separated from the catalyst and catalyst is recoverable without being its activity reduced. These catalysts have extremely strong proton acid sites and inherently they have more catalytic activity than conventional catalysts [18].

Reaction in the water is one of the main challenges and objectives of the organic molecules reaction, since it is cheaper and safer in comparison with organic solvents and it reduces the use of harmful organic solvents and leads to the development of environmentally friendly chemical processes. However, academic and industrial chemists still use water instead of organic solvents for two main reasons. First, many organic materials are insoluble in water and consequently water is not as a conductive reaction function. Second, many of the reagents, reaction substrates and catalysts are decomposed or disabled by water. Some of these problems solved with the discovery of water tolerant Lewis acids by Kobayashi et al. However, it is essential to synthesis new types of inexpensive and powerful watery active Lewis acids [19].

In fact, the high catalytic activity (high yield, short reaction time, and under mild reaction conditions), the applicability of green energy sources, for instance, ultrasound irradiation, as well as the facile recyclability over many consecutive reactions, economical, clean and practical are the prominent demands in the development of new heterogeneous catalyst [16, 20]. In recent years much research has been conducted for the synthesis of bisindolylmethane. Each of the used methods and catalysts has advantages and disadvantages. Synthesis of bisindolylmethane production reactions by using different catalysts are presented in articles under different temperature conditions and various solvents. The overall reaction is as the figure 1.

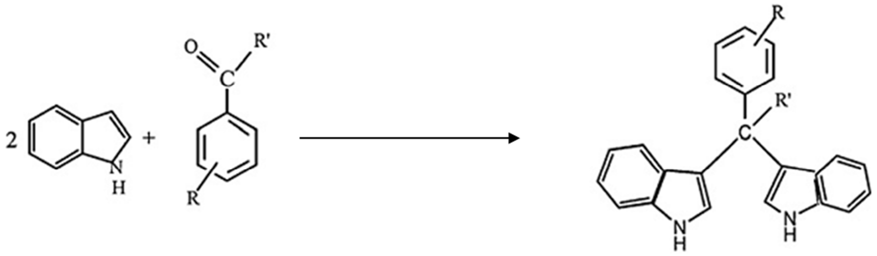

Figure 1. *The overall reaction.*

R could be alkyl, halogen, hydroxyl, nitro, methoxyl, etc. And R' could be hydrogen or methyl. As previously mentioned various catalysts used for synthesis, each of them had advantages and disadvantages. Some disadvantages of some catalysts are the impossibility of recycling the catalyst, long reaction time, low efficiency, toxicity, and the separation problems of the catalyst from the product. The experimental method is that indole with a ratio of 2:1, added to the aldehyde. In all the articles that had been studied if there was solvent, the reaction had been done in the reaction vessel as glassy balloons or etc. That it was stirred constantly. Stirring often had been done by a magnet. When the reaction was in solvent-free conditions, it had been done in the mortar and pestle. Also temperature condition was different in presence of the various catalysts. Reaction completion was measured by TLC. After completion of the reaction, catalyst was recovered, and product purification was done in the most cases. Commonly purification was performed by column chromatography. The points of melting, HNMR, CNMR, IR and mass measurement were used for characterization of products. In this study I_2 was used as a catalyst in solvent-free conditions due to easy separation and low reaction time.

2. Method

2.1. Bisindolyl Methane Production Method on Solid - Solid State

In this reaction, one mmol of indole, 0.5 mmol of desired aldehyde and catalyst were added to the reactor along with ball, after a reaction time at a given frequency, the material was removed from the reactor. At this point it could be picked up some of it to TLC test. Ethanol was used to dissolve materials, in case of non-resolution the MDF was used for dissolving. Ethyl acetate and n-hexane were used in the ratio of 3: 1 to display the chromatogram. Initially, materials inside the reactor dissolved in ethyl acetate for the purification of the reaction, and also solved sodium thiosulfate in distilled water and then both dumped decantation, then it stirred up that the iodine content in the organic phase forming the salt with sodium thiosulfate and it got into the watery phase. Then the valve decantation opened until the aqueous phase went out. The organic phase was poured in glass and it placed 24 hours in an oven at 40 °C to evaporate the solvent. Then it was dissolved in a minimum ethyl acetate and n-hexane added drop by drop to precipitate was formed. Finally, sediment was removed and after the drying mass was measured to calculate efficiency.

2.2. The Introduction of the Reciprocating Manufacturer Machine

One device was used for the production of the reciprocating motion in this study. The device is based on the crank mechanism. The mechanism is used for converting rotational motion into linear motion or vice versa. It creates high rotational speed and range of motion to the desired reaction. It can operate at different frequencies. It creates the reciprocating motion to 70 Hz (4000 rpm) and the range of motion of 12 cm for the reactor. The reactor is made of stainless steel. From the thermometers (testo) Terminator TIR 8859 has been used to review the reactor temperature in the reactor protective casing. A cooling fan is also designed for the reciprocating manufacturer machine and reactor. Schematic of machine design is given in figure 2. And the numbers on the figure are the major constituents of the reciprocating device.

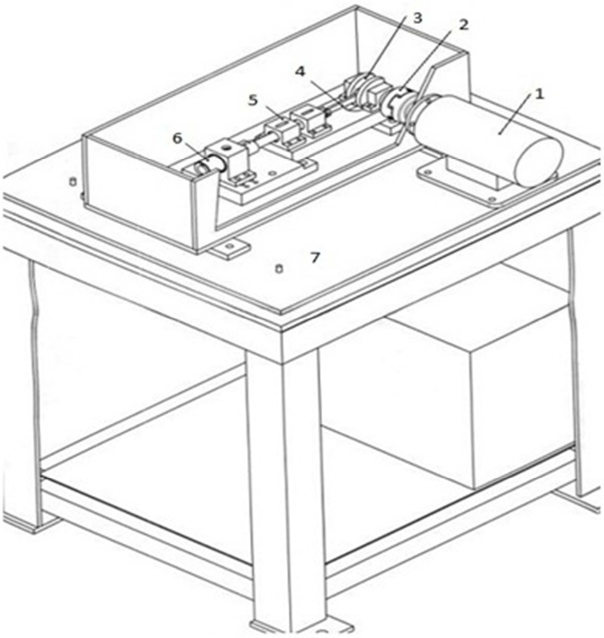

Figure 2. Schematic of the reciprocating machine design. 1) The electric motor (3 kW). 2) coupling, 3) Crankshaft, 4) The connecting rod, 5) Bearing, 6) The chamber that the capsule or reactor is placed in it. 7) Chassis.

Figure 3 is the final shape of device.

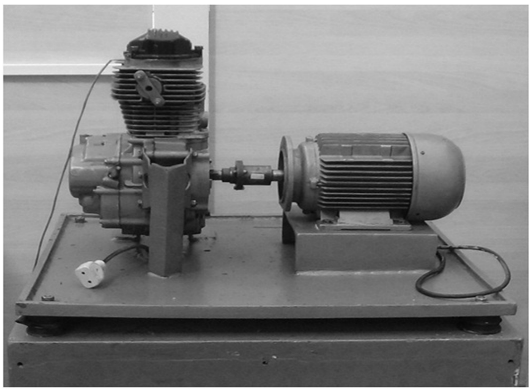

Figure 3. The final form of the reciprocating manufacturer motion without a protection device.

Capsule or the reactor that placed inside the reciprocating device is made of stainless steel, with 14 mm inner diameter. Maximum diameter of balls is 6mm that placing in the reactor. The main problem is control and torque tolerance created on the death points, (In every round of rotation, necessarily a sweep happens and there is one death point at the beginning and the end of the crank shaft). Dimension of reactor and ball is shown in the figure 4.

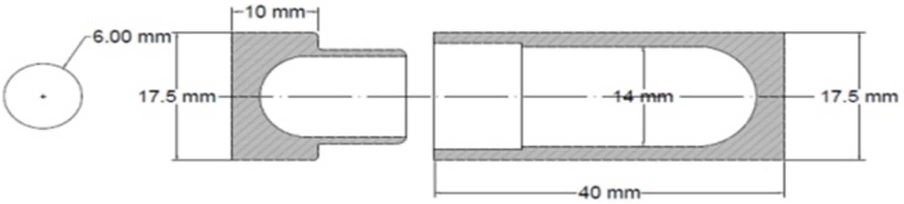

Figure 4. Dimension of reactor and ball.

Figure 5 shows capsules or reactor that placed in the reciprocating machine.

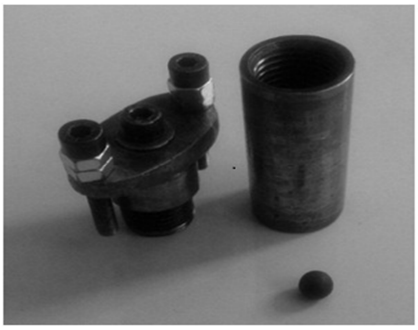

Figure 5. The final shape of reactor.

2.3. The Machine Rapid at Different Frequencies

As the engine speed is 2840 rpm and network frequency is 50 Hz, the RPM at any frequency can be achieved according to the proportional relationship:

$$50 / f * 2840 = \text{amount of the rapid at frequency } f \quad (1)$$

So the rapid of machine at the used frequencies is as table 1:

***Table 1.** Amount of the used rapids at different frequencies in the experiments.*

Frequency (Hz)	5	10	20	30	40	50
RPM	284	568	1136	1704	2272	2840

2.4. Theory and Calculation

2.4.1. The Reaction Mechanism

As it can be observed in figure 6 The most probable mechanism for this reaction is as follows that first, The catalyst, activates the carbonyl group of the aromatic aldehyde to give intermediate a, and then a attacked the indole and an electrophilic substitution reaction is done at the C-3 of indole a to give b and loss H_2O from b. It affords c from b, which is activated by iodine. The other indole is added to c in the following step to give the TM (d) and it loses molecular iodine, which can catalyze the reaction in a catalytic manner [10].

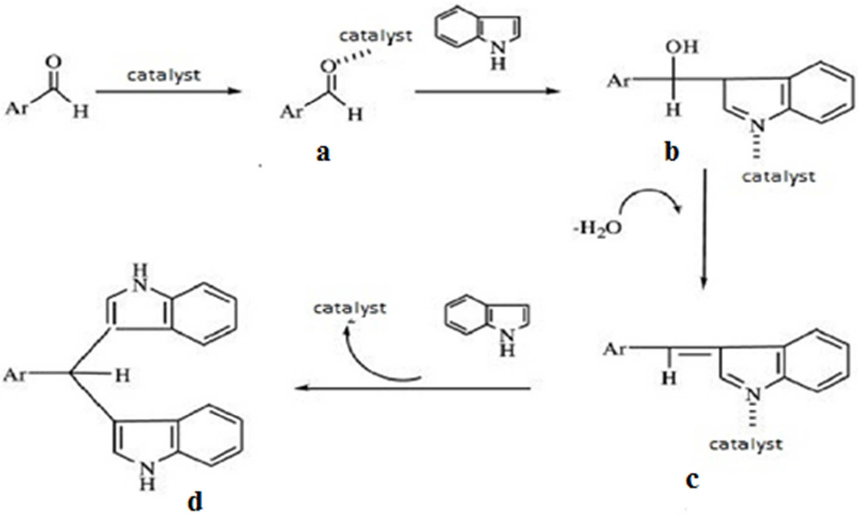

Figure 6. The probably mechanism for reactions of indoles with various aromatic aldehydes [10].

2.4.2. Check the Progress of the Reaction by Using TLC Techniques

In this study, TLC technique was used to determine the reaction completion. For this purpose, the silica coated onto thin sheet of aluminum was used that it had been purchased. It often can be used after preparation of the pure product or product with impurities. In this study, often the progress of the reaction was checked by TLC after and before of purification. Usually some of the pure raw material used in alongside of product to distinguish one product from raw material. Since inorganic components will remain at the base, therefore, identifying organic components is possible by having pure reactant materials. This is an optimized method of solvent system; the used solvents in this study are; n-hexane as a non-polar solvent and ethyl acetate as a polar solvent. First, the non-polar solvent was used and it was observed that there was no separation on TLC plate. Then, the percentage of polarity increased by increasing the amount of ethyl acetate solvent. In conducted experiments by pouring 15 drops of n-hexane and 5 drops of ethyl acetate the separation of the two spots was well within reach. Figure 7 shows the results of investigations by TLC. Figure 7 is related to indole and 4-chloro benzaldehyde reaction. The spots are indole, 4-chloro benzaldehyde, resulting compound after 5 minutes with a frequency of 5 Hz, resulting compound after 15 minutes with a frequency of 8 Hz, and the product after purification, respectively, from left to right. As it could be observed after 5 minutes and 5 Hz the reaction was not completed and there was still the reactant in the reaction mixture. It was visible because there were 3 spots. In the event that the reaction was completed in the next section because there was only one spot after 15 minutes with a frequency of 8 Hz. Finally, absence of the spots at the base represented the purity of the sample.

Figure 7. *Check the progress of the reaction of Indole and 4-chlorobenzaldehyde by TLC.*

3. Result

In this study the reaction between two aldehyde and indole was investigated in the reciprocating reactor. It was the reaction condition that ball impact was investigated at two different times and two different frequencies 5 and 8 minutes, 5 and 8 Hz. The reaction was carried out at room temperature and under solvent free condition. Considering the completion time of the reaction, analysis was performed before the end of the reaction, so that the effects of parameters were evident. Four two-millimeter balls were used at different stages. One, two, three and four balls entered in to the reactor, respectively. According to data provided in the articles and things that had been done in this field, previously, and also limitation of the amount of available reactants, time, frequency, aldehyde, number and type of balls parameters were studied. After obtaining the data, tests and procedures were designed given the number of variables and by using Minitab software. Presentations are in table 2.

Table 2. *Presentations.*

Aldehyde type	Reaction time (Min)	Number of balls	Frequency (Hz)
4-cholorobenzaldehyde	5	1	5
3-nitrobenzaldehyde	5	1	5
4-cholorobenzaldehyde	5	2	5
3-nitrobenzaldehyde	5	2	5
4-cholorobenzaldehyde	5	3	5
3-nitrobenzaldehyde	5	3	5
4-cholorobenzaldehyde	5	4	5
3-nitrobenzaldehyde	5	4	5
4-cholorobenzaldehyde	8	1	5
3-nitrobenzaldehyde	8	1	5
4-cholorobenzaldehyde	8	2	5
3-nitrobenzaldehyde	8	2	5
4-cholorobenzaldehyde	8	3	5
3-nitrobenzaldehyde	8	3	5
4-cholorobenzaldehyde	8	4	5
3-nitrobenzaldehyde	8	4	5
4-cholorobenzaldehyde	5	1	8
3-nitrobenzaldehyde	5	1	8
4-cholorobenzaldehyde	5	2	8
3-nitrobenzaldehyde	5	2	8
4-cholorobenzaldehyde	5	3	8
3-nitrobenzaldehyde	5	3	8
4-cholorobenzaldehyde	5	4	8
3-nitrobenzaldehyde	5	4	8
4-cholorobenzaldehyde	8	1	8
3-nitrobenzaldehyde	8	1	8
4-cholorobenzaldehyde	8	2	8
3-nitrobenzaldehyde	8	2	8
4-cholorobenzaldehyde	8	3	8
3-nitrobenzaldehyde	8	3	8
4-cholorobenzaldehyde	8	4	8
3-nitrobenzaldehyde	8	4	8

All experiments were repeated twice. The total 64 tests were performed and even though it was tried to minimize all laboratory errors, but laboratory errors are an integral part of laboratory work. Data are in table 3. Number 2 is repeated the experiment number 1. Reactions were as follows;

$$2C_8H_7N + C_7H_5Cl \rightarrow C_{23}H_{17}ClN_2 + H_2O \tag{2}$$

$$2C_8H_7N + C_7H_5NO_3 \rightarrow C_{23}H_{17}N_3O_2 + H_2O \tag{3}$$

Table 3. *Data obtained from experiments.*

efficiency percent of the reaction of 4-cholorobenzaldehyde	efficiency percent of the reaction of 3-nitrobenzaldehyde	Time (min)	Frequency (Hz)	The number of ball	Experiment
16.85	21.24	5	5	1	1
17.08	20.35	5	5	1	2
22.47	24.87	5	5	2	1
22.35	24.5	5	5	2	2
29.77	35.23	5	5	3	1
29.9	33	5	5	3	2
15.73	25.9	5	5	4	1
14.06	25.9	5	5	4	2
25.28	37.3	8	5	1	1
24.5	37.5	8	5	1	2
28.08	46.63	8	5	2	1
29	46	8	5	2	2
38.76	51.8	8	5	3	1
38.76	51.85	8	5	3	2
29.21	44.04	8	5	4	1
29.7	45	8	5	4	2
25.28	45.07	5	8	1	1
23.16	44.87	5	8	1	2
32.58	48.18	5	8	2	1
32.05	47	5	8	2	2
56.18	52.84	5	8	3	1
56.6	53	5	8	3	2
28.1	38.86	5	8	4	1
28.39	38.86	5	8	4	2
39.32	58.03	8	8	1	1
39.32	55	8	8	1	2
48.87	61.13	8	8	2	1
49	60.75	8	8	2	2
70.78	72.53	8	8	3	1
68	72.8	8	8	3	2
46.06	55.95	8	8	4	1
45	55.55	8	8	4	2

Table 4 has the results that it has been done in some of the papers previously.

Table 4. *Results in some of the papers previousl.*

Reaction condition	Reaction time	Reaction time	Efficiency (3-nitrobenzaldehyde)	Efficiency (4-cholorobenzaldehyde)	catalyst
	3-nitrobenzaldehyde	**4-cholorobenzaldehyde**			**year**
Solvent free Room temperature	8 hr	8.5 hr	0.83	0.7	Zeokarb 225 2004 [21]
Solvent free 50°C.	-	45 min	-	0.94	Mn/ZrO$_2$-450 2013 [22]
Room temperature	45 min	30 min	0.92	0.97	HFIP [1][1] 2011 [14]
CH$_3$CN	10 min	10 min	0.98	0.97	PFPAT[2] 2011 [9]
Room temperature Solvent free	-	8 min	-	0.91	I$_2$ 2004 [17]
10°C Dicholoro methane	4 hr	5 hr	0.72	0.64	Zeolite 2004 [2]

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[1] 1,1,1,3,3,3-hexafluoro-2-propanol

[2] Pentafluorophenilammoniumtriflate

As it is shown in table 4, for some catalysts such as Zeokarb -225 and zeolite reaction time is too long. In this study, we tried to reduce the reaction time and the reaction was done faster. Reaction time had been reduced to ten minutes by using PFPAT catalyst, but CH_3CN was used as solvent. The purpose of this study is solvent-free reaction condition. In the presence of Mn/ZrO_2-450, 50°C it was also needed to reduce the reaction time to 45 minutes. In one of the tasks performed by Sareh Bayat in the transport phenomena center, reaction time had been greatly reduced with increasing frequency very high doses. The sharp rise in frequency increased machine volatility greatly, so it was not safe. Security is one of the most important parameters in the industry. The results are according to table 5 for 40 Hz. In this study, the highest yield was obtained at time of 8 minutes and frequency of 8 Hz. Achieved reaction time and efficiency were safer and more reasonable.

Table 5. *Time and efficiency for reactions with frequency of 40 Hz.*

Aldehyde type	Reaction time	Yield
3-nitrobenzaldehyde	1 min	0.87
4-cholorobenzaldehyde	1.5 min	0.91

4. Discussion

4.1. Effects of All Parameters

The effects of time, frequency and the number of balls were investigated for the tests with adjust ss.

Table 6. *The effects of parameters with adjust ss.*

Source	DF	Seq SS	Adj SS	Adj MS	F	P
Ball	3	2943.25	2943.25	981.08	1702.16	0.000
Time	1	3470.24	3470.24	3470.24	6020.79	0.000
Frequency	1	5018.13	5018.13	5018.13	8706.34	0.000
Aldehyde	1	1713.24	1713.24	1713.24	2972.42	0.000
Ball*time	3	32.77	32.77	10.92	18.95	0.000
Ball*frequency	3	253.29	253.29	84.43	146.48	0.000
Ball*aldehyde	3	204.42	204.42	68.14	118.22	0.000
Time*frequency	1	8.02	8.02	8.02	13.91	0.001
Time*aldehyde	1	83.97	83.97	83.97	145.69	0.000
Frequency*aldehyde	1	2.29	2.29	2.29	3.98	0.055
Ball*time*frequency	3	3.83	3.83	1.28	2.21	0.106
Ball*time*aldehyde	3	23.87	23.87	7.96	13.80	0.000
Ball*frequency*aldehyde	3	211.92	211.92	70.64	122.56	0.000
Time*frequency*aldehyde	1	87.87	87.87	87.87	152.45	0.000
Ball*time*frequency*aldehyde	3	43.82	43.82	14.61	25.34	0.000
Error	32	18.44	18.44	0.58		
Total	63	14119.36				

S =0.759195, R-Sq=99.87%,
R-Sq(adj) =99.74%

Table 6 shows the importance of the used variables that p value and f factor show the most effective parameters. The importance of variable is higher when it has the smaller p and larger f. P of variables that is larger than 0.05, are much less important that its impact can be ignored. These included investigating the effects of aldehyde* frequency and ball* frequency * time that they had little effect. When p is zero, parameters are important and they affect the output variables. Then f factors should be compared to each other. Each f is higher than others, that it is more important and more effective in output variable. By comparing the results, it could be seen that the ball, time, frequency and aldehyde were more important than others. And among them frequency was the most effective. With increasing frequency, the reactant materials were disturbed faster and then were smaller, and their contact area increased. The reaction speed was increased by increasing contact area and reaction conversion percentage increased, reaction completion times reduced and reacted faster.

4.2. Distribution and Accuracy of Data

These charts illustrate the accuracy and distribution of data.

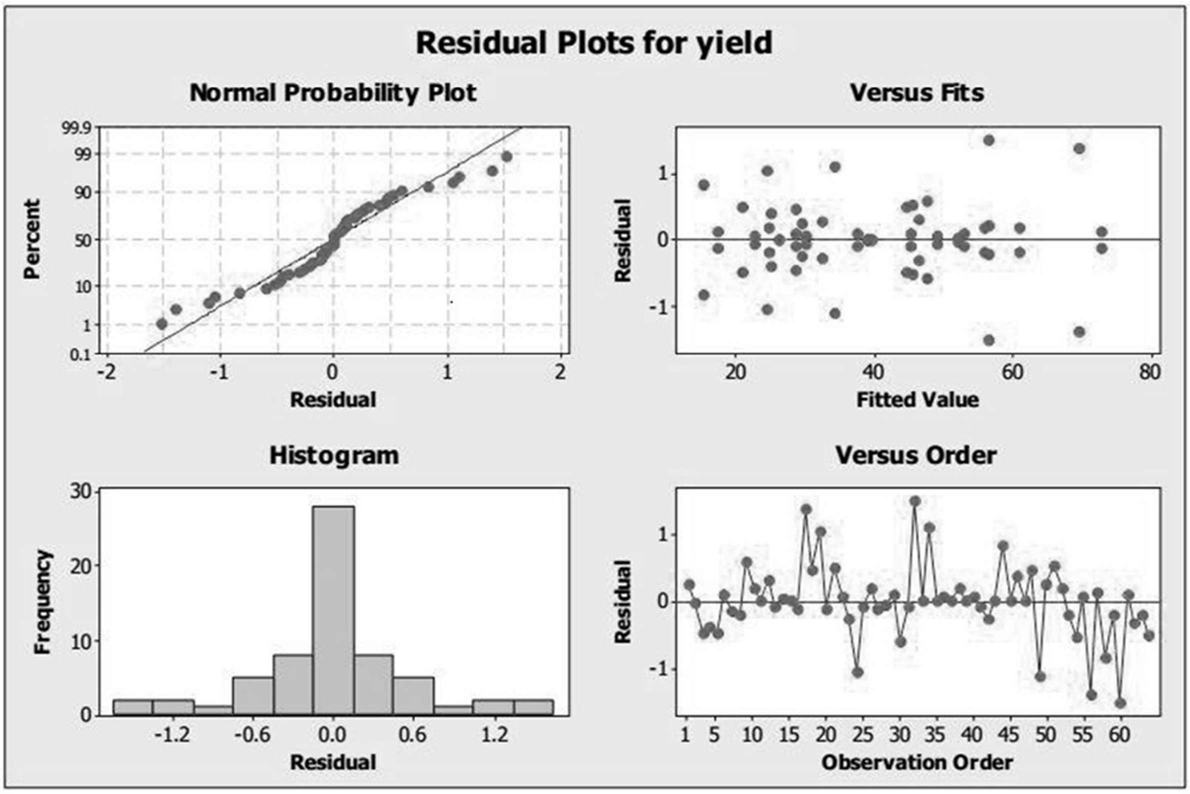

***Figure 8.** Scatter plots data.*

Charts of figure 8 show the accuracy and scatter of data. According to this chart, it could be said that experiments had been conducted with a good scattering and the results of data could be trusted.

Versus fits showed the remaining amounts of discrepancies of data from the average value. All data were added together and divided into the number of data and a mean value was obtained. Data that difference was more than two with average value they were of outlier's data. As it could be seen more data were close to zero residual value. Versus fits showed the suitable dispersion of data.

Normal probability graph showed that the remaining values had more density around the zero. And they were very close to the right line. Histograms showed appropriate distribution of data.

How to read a histogram and in practice it is used? To this end, the following is remarkable:

1) Distribution pattern: with observing a histogram usually can be check these out.
    A) Abundance: in the above example could be said to answer this question; obviously, the highest column of histogram showed the highest abundance.
    B) Dispersion extent: due to the size (width and slimmer), it can be judged on the distribution extent. In the above example, it could be seen optimal dispersion.
    C) For symmetric distributions: according to the histogram; one can conclude that if there is symmetric distribution or not? And thus statistical properties inferred.
    D) Distorted distribution: clearly, any curvature of the distribution can be detected with respect to the histogram.
    E) Distribution peak: if there is a peak in the histogram and this summit is not about the production standard average; in this case, it is clear that production, mainly, is carried away from the standard levels. This is the important point that deserves attention.
2) The sloping histogram: usually, sloping histogram is unusual and it indicates a problem in work.
3) The serrated histogram: in general, the indentation of the histogram is unusual and a sign of trouble in work, in most cases, this problem can be from measuring equipment or process operations.
4) Compare the histogram with acceptable limits: it should be determined production acceptable limits in the histogram. These points should be noted in this comparison that if the products are matching with acceptable limits? Otherwise, the percentage of products outside the scope of what it is acceptable, should be seen. Are averages right in the center of acceptable limits? Otherwise, differences should be determined and evaluated.
5) Comparison of the histograms: over time and during process, the quality of products histograms can be compared and so found establish of desired production or defects development in production.
6) Discontinuities in the histogram: usually, discontinuities in the histogram indicate abnormal factors of production.

4.3. Interactions Between Variables

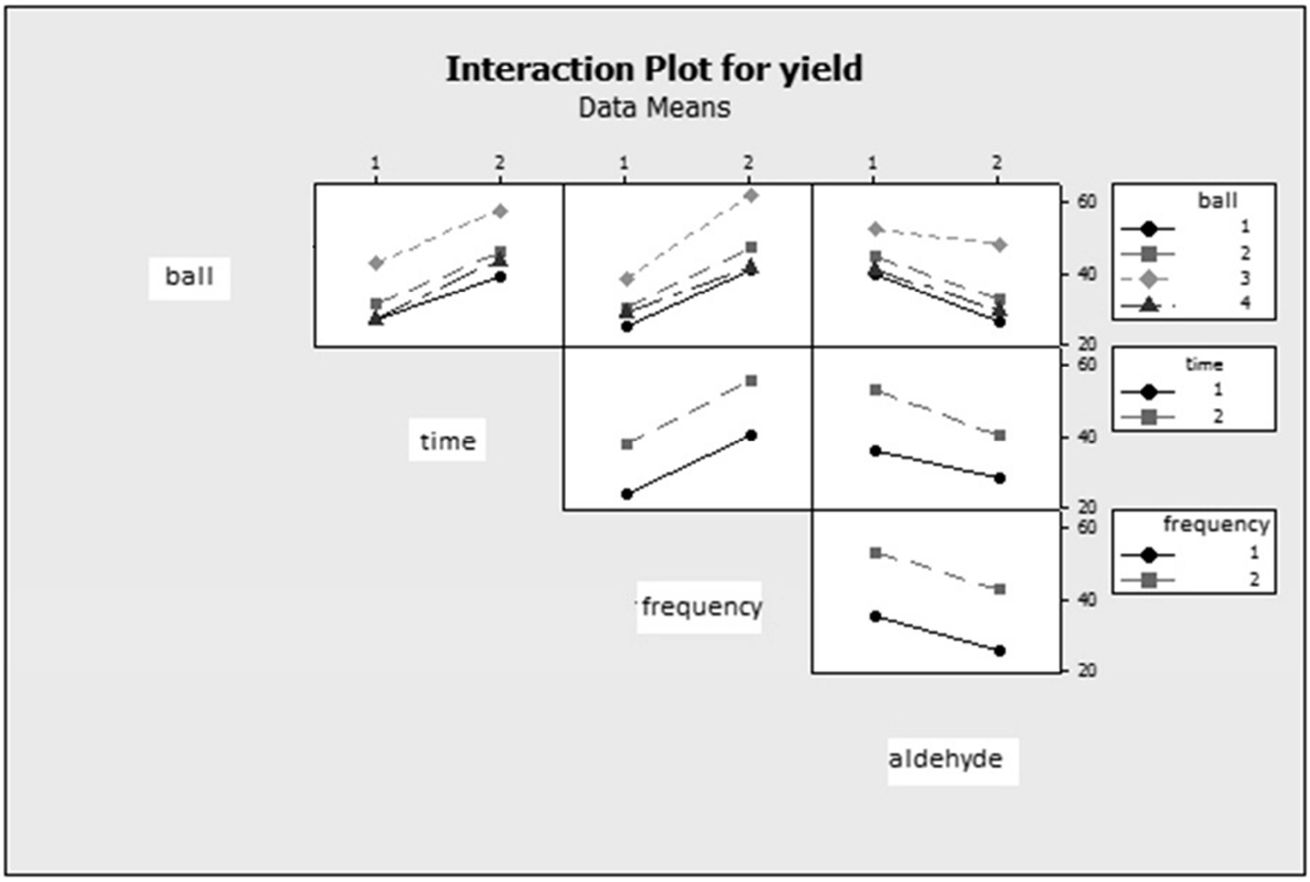

Figure 9. The interactions between the variables.

Diagrams in figure 9 show the interactions between the variables that which is more important and influential. Each of the curves that intersector closer to each other was more important. And whatever the distance between the curves increased the importance of parameter was reduced. Also, it could be interpreted analyze of the charts in table 6, that whatever f was higher, among the transactions distance between these charts was also less.

Right vertical axis in the above diagrams showed the conversion percentage. Respectively, bottom to top, in the bottom graph horizontal axis was aldehyde and the left vertical axis was frequency. On the horizontal axis number one was 3-nitrobenzaldehyde, and number two was 4-cholorobenzaldehyde. With the increasing frequency of 5 Hz (1 line), to 8 Hz (2 line) yields increased for both aldehyde. In the second row, time was left vertical axis, horizontal axis was aldehyde and frequency, respectively, from right to left. In the diagram, yield for both aldehydes increased with increasing time of 5 minutes (1 line), to 8 minutes (2 line). In middle row on the left diagram, slope of the curve changed. On the horizontal axis number one was 5 Hz and number two was 8 Hz. Each of number 2 and number 1 lines showed 5 minutes and 8 minutes respectively, at the constant time efficiency increased with increasing frequency. The efficiency increased with increasing frequency and time at the same time. In top row from right to left efficiency was checked for, aldehyde type and ball, frequency and ball, time and ball according to their effects at the same time. For all three parameters, efficiency increased by increasing the number of balls to 3 but efficiency reduced by adding the fourth ball. With 4 balls efficiency decreased because of reducing space to move the balls and reactant material that it reduced the amount of mixing. According to the above description, it could be seen that the impact of ball and frequency on the efficiency was higher than the rest and also aldehyde and time had a significant impact on the efficiency at the same time.

4.4. Main Effects Plot for Yield

In figure 10 the vertical axis of the diagram shows the efficiency that it could be determined at any diagram which showed a higher efficiency in each variable. For example, the time plot had two levels that number one caused efficiency less than number two. In the ball diagram, the efficiency increased by increasing the number of balls to 3, but the efficiency decreased by 4 balls as mentioned above. The efficiency increased with an increase of frequency 5 to 8 Hz. And at the end the efficiency of the reaction of indole and 3-nitrobenzaldehyde was more than 4-chlorobenzaldehyde and indole.

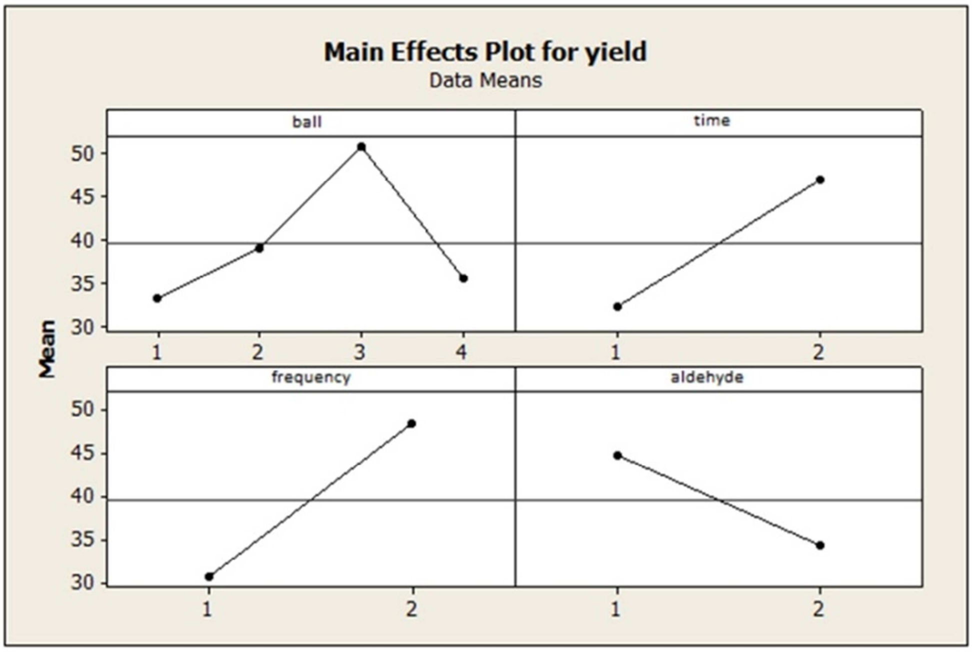

Figure 10. *Main effects plot for yield.*

4.5. Analysis

Figure 11. *Melting point device IA9200 Model.*

For product identification color test, determining the melting point, FT-IR and HNMR analysis were used. The conducted reaction product color was pink in accordance with references that the color of the product was obtained in laboratory conditions, too. To determine the melting point in laboratory conditions, it can be used an oil bath and a thermometer or the device can determine the melting point IA9200 model or use the TG analysis. Here the machine was used to determine the melting point. The product melting point of indole and 3-nitrobenzaldehyde reaction had been measured about 220°C that it was according to the references. Reported melting point for 3,3’-bisindolyl-(3-nitro phenyl)methane is about 219-221°C in references. Melting point of 4-chlorobenzaldehyde with indole reaction product was measured about 70°C. Reported melting point for 3,3’-bisindolyl-(4-cholorophenyl)methane was about 76-77°C in references. Because of this difference in temperature HNMR analysis was used that showed the reaction product of indole and 4-cholorobenzaldehyde was the same 3,3'-bisindolyl- (4-chloro phenyl) methane. Determining melting point device is given in figure 11.

4.5.1. FT-IR Analysis

FT-IR analysis was used to determine the functional groups on the surface of produced bisindolylmethane. The analysis of the samples was conducted by UNICAM 4600, Mattson 1000 model, at Sahand University that it is shown in figure 12.

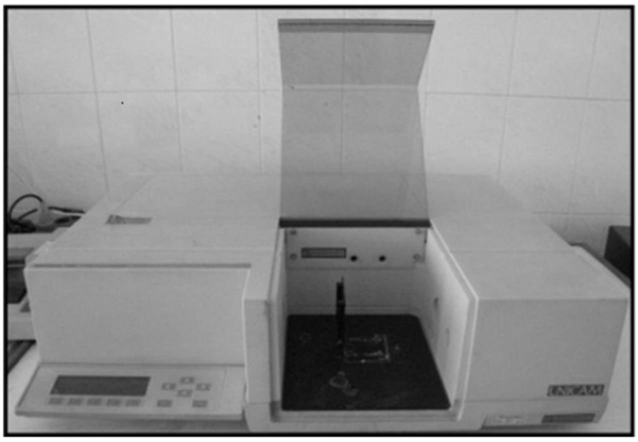

Figure 12. *FTIR device used to detect bisindolylmethane surfacegroups.*

Figure 13 shows, FT-IR spectrum of the synthesis of 3,3'-bisindolyl- (3-nitro-phenyl) methane and 3,3'- bisindolyl- (4-chloro phenyl) methane materials.

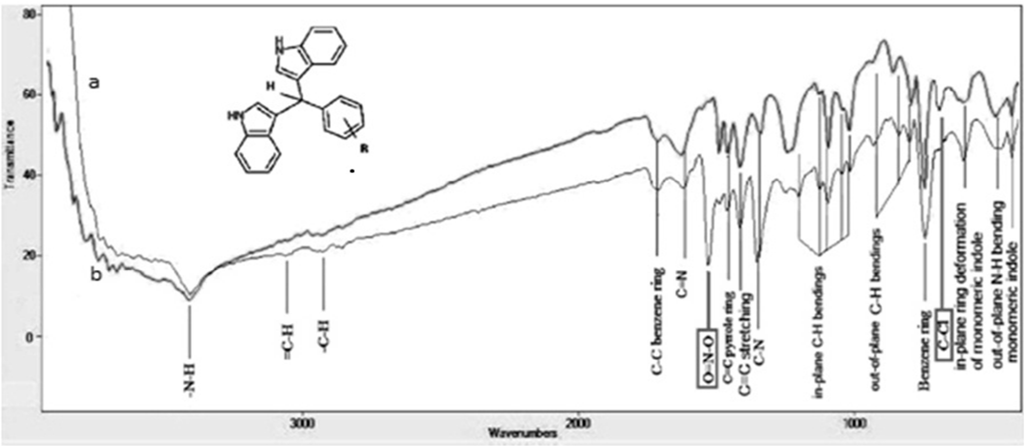

Figure 13. *FTIR spectra of the reaction of 4-chlorobenzaldehyde (b) and 3-nitrobenzaldehyde (a) with indole.*

Absorb stretching of carbonyl group is one of the strongest absorption in IR. The strong peak to the aldehyde carbonyl happens in the range of 1690-1740 cm^{-1}. The absence of this peak represents the reaction. There were peaks in 3413cm^{-1} wavelength because of the -N-H group and in 2922 cm^{-1} and 3049 cm^{-1} wavelengths because of the = C-H, and -C-H groups. Also, there were peaks in 1717, 1630, 1463, 1416, 1351 cm^{-1} wavelengths, respectively, which represented the flexural vibration of C-C in the ring, C-N, C = C Groups in the pyrrole ring, stretching vibration of C = C and C-N' group.

Peaks in the range of 1000 to 1250 cm^{-1} wavelength were flexural vibrations of C-H on the page and those who were in the range of 800 to 950 related to the flexural vibrations out of the page. Peak in the 750 cm^{-1} wavelength was the benzene ring and the peaks 606, 487 and 429 cm^{-1} wavelength were related to monomer deformation inside the indole ring and flexural vibrations of N-H and monomer indole outside the page, respectively.

Unique peaks in 1528 and 696 cm^{-1} wavelengths showed two different groups -NO2 and C-Cl which corresponded to the difference between the aldehyde was used to synthesize. As a result, according to this analysis, it could be said the final product was earned in both syntheses.

4.5.2. (300 Mz, $CDCl_3$)^{1}H NMR Analysis

The spectrum of product resulting from the reaction of indole and 4-chlorobenzaldehyde has been brought in figure 14. As could be seen HNMR spectrum of the product contains four spades. A single branch peak appeared in 83/5 (ppm) was related to CH protons of benzyl in the loop. A single branch peak appeared in 57/6 (ppm) was related to CH protons of indole and one broad branch peak in 84/7 (ppm) was the indole NH. Protons of aromatic rings had been appeared in 35.7-98.6 (ppm) area. Also, the sum of the numbers shown on the integral indicators was the number of hydrogen available on the product. According to figure 14 this amount was equal to 17.93 that it was matched with 17 hydrogens in the structure of 3,3'- bisindolyl (4-Chloro-phenyl) methane.

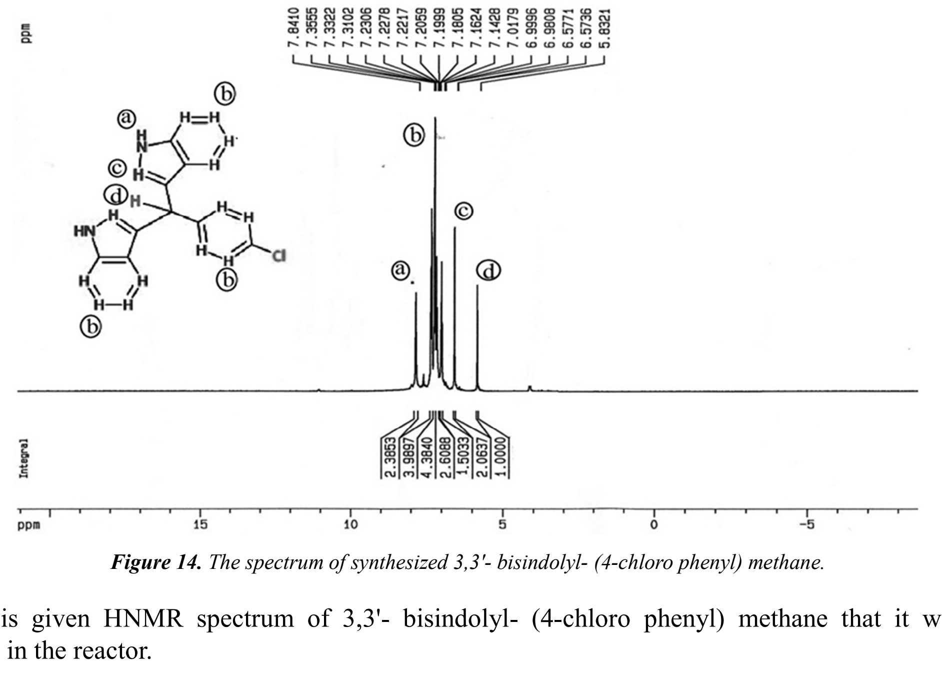

Figure 14. *The spectrum of synthesized 3,3'- bisindolyl- (4-chloro phenyl) methane.*

Also, figure 15 is given HNMR spectrum of 3,3'- bisindolyl- (4-chloro phenyl) methane that it was match with the synthesized product in the reactor.

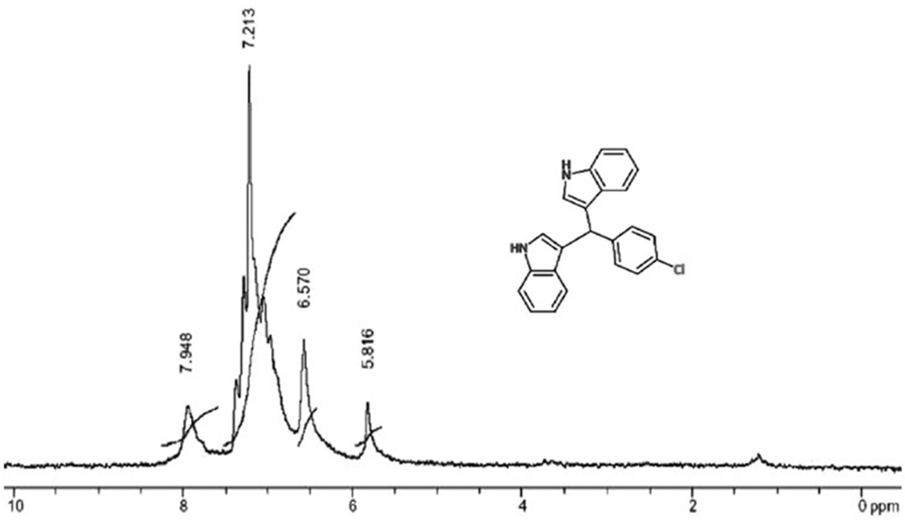

Figure 15. *The spectrum of 3,3'- bisindolyl- (4-chloro phenyl) methane.*

5. Conclusion

Nowadays, a lot of researches are done in order to provide the right guide for chemical processes that can be reached to the appropriate methods to provide the high efficiency in less time without using the dangerous organic solvents. The best way to prevent the presence of harmful solvents to the environment is using the optimal production methods that it has the lowest pollution in the environment. One of these strategies is solid-solid reaction without the presence of solvent.

To do take better chemical reactions it is necessary for raw material to be together every moment and for this purpose reactor design must be such that it can be created a homogeneous mixing in all parts of the reactor. For this purpose, reciprocating reactor had been used in this study.

In this study, the reaction between the indole and aromatic aldehydes without solvent, in the presence of iodine catalyst was investigated to produce bisindolylmethane. Aldehydes were including 3-nitrobenzaldehyde and 4-cholorobenzaldehyde. Reactions were performed at room temperature. Reactant materials and products were in Solid-phase. For this reason, the high-speed reciprocating reactor was used for mixing the reactants in the solid state. Previous studies had shown that the frequency had the greatest impact on useful yields. Color test, the melting point determination, FT-IR analysis, and HNMR analyzes were used for product identification. The color of the obtained product was Pink that it matched with references. It was used to detect the reaction that the carbonyl group of aldehyde must be eliminated during the reaction. Absorb stretching of carbonyl group is one of the strongest absorption in IR. The strong peak to the aldehyde carbonyl happens in the range of 1690-1740 cm^{-1}. The absence of this peak represents the reaction done.

HNMR spectrum was prepared from the product resulting of the indole and 4-chloro benzaldehyde reaction in the reactor. HNMR spectrum of the product contained four spades. A single branch peak appeared in 83/5 (ppm) was related to CH protons of benzyl in the loop. A single branch peak appeared in 57/6 (ppm) was related to CH protons of indole and One broad branch peak in 84/7 (ppm) was the indole NH. Protons of aromatic rings had been appeared in 35.7-98.6 (ppm) area. Also the sum of the numbers shown on the integral indicators is the number of hydrogen available on the product. According to figure 14 This amount was equal to 17.93 that it was matched with 17 hydrogens in the structure of 3,3'- bisindolyl (4-Chloro-phenyl) methane.

References

[1] Meysam Baghbanian, S., Babajani, Y., Tashakorian, H., Khaksar, S., Farhang, M., (2013). "p-sulfonic acid calixarene: An efficient reusable organocatalyst for the synthesis of bis(indolyl)methanes derivatives in water and under solvent-free conditions". Comptes Rendus Chimie, 16, 129–134.

[2] Karthika, M., Tripathi, A. K., Gupta, N. M., Palanichamy, M., Murugesan, V., (2004). "Zeolite catalyzed electrophilic substitution reaction of indoles with aldehydes: synthesis of bis(indolyl)methanes". Catalysis Communications, 5, 371–375.

[3] Swapna S. Mohapatra, Zoe E. Wilson, Sujit Roy, Steven V. Ley, (2017). "Utilization of flow chemistry in catalysis: New avenues for the selective synthesis of Bis(indolyl)methanes". Tetrahedron, 73, 1812-1819.

[4] Sayed Hossein Siadatifard, Masumeh Abdoli-Senejani, Mohammad Ali Bodaghifard, (2018). "An efficient method for synthesis of bis(indolyl)methane and di-bis(indolyl)methane derivatives in environmentally benign conditions using TBAHS". Organic chemistry/ research article, cogent chemistry.

[5] Kovuru Gopalaiah, Sankala Naga Chandrudu, Alka Devi, (2015). "Iron-Catalyzed Oxidative Coupling of Benzylamines and Indoles: Novel Approach for Synthesis of Bis(indolyl)methanes". Special Topic, Synthesis.

[6] Hamid Dezhampanah, Masoomeh Esmaili, Alireza Khorshidi, (2017). "A combination of spectroscopic and molecular docking techniques to study interaction of bis(indolyl)methane with bovine milk α-casein". International Journal of Food Properties, 2686–2698.

[7] Shirini, F., Ghaffari Khaligh, N., Goli Jolodar, O., (2013). “An efficient and practical synthesis of bis(indolyl)methanes catalyzed by N-sulfonic acid poly(4-vinylpyridinium) chloride”. Dyes and Pigments, 98, 290-296.

[8] Ji-Tai Li, Ming-Xuan Sun, Gen-Ye He, Xiao-YaXu, (2011). “Efficient and green synthesis of bis(indolyl)methanes catalyzed by ABS in aqueous media under ultrasound irradiation”. Ultrasonics Sonochemistry, 18, 412–414.

[9] Khaksar, S., Mojtaba Ostad, S., (2011). “Pentafluorophenylammoniumtriflate as an efficient, environmentally friendly and novel organocatalyst for synthesis of bis-indolylmethane derivatives”. Journal of Fluorine Chemistry, 132, 937–939.

[10] Yong Lei Yang, Ning Ning Wan, Wen Ping Wang, Zheng Feng Xie, Ji De Wang, (2011). “Synthesis of bis(indolyl) methanes catalyzed by Schiffbase–Cu(II) complex”. Chinese Chemical Letters, 22, 1071–1074.

[11] Praveen, C., Dheen Kumar, P., Muralidharan, D., Perumal, P. T., (2010). “Synthesis, antimicrobial and antioxidant evaluation of quinolines and bis(indolyl)methanes”. Bioorganic & Medicinal Chemistry Letters, 20, 7292–7296.

[12] Sharma, G. V. M., Janardhan Reddy, J., Sree Lakshmi, P., and Palakodety Radha Krishna, (2004). “A versatile and practical synthesis of bis(indolyl)methanes/bis(indolyl)glycoconjugates catalyzed by trichloro-1,3,5-triazine”. Tetrahedron Letters, 45, 7729–7732.

[13] Karami, Ch., Ahmadian, H., Nouri, M., Jamshidi, F., Mohammadi, H., Ghodrati, K., farrokhi, A., Hamidi, Z., (2012). “A novel method for synthesis of cobalt manganese oxide nano catalysts as a recyclable catalyst for the synthesis of some bis (indolyl) methane derivatives”. Catalysis Communications, 27, 92–96.

[14] Khaksar, S., Mohammadzadeh, S., (2011). “A simple, efficient and green procedure for the synthesis of bis-indolylmethanes in 1,1,1,3,3,3-hexafluoro-2-propanol”. Journal of Fluorine Chemistry, 135, 87–90.

[15] Teslima Dasbasi, Sidika Polat-Cakir, Meysun Abdullah, Ayhan S. Demir., (2011). “Indium triflate-catalyzed coupling of indoles with acyl phosphonates: synthesis of bis(indolyl)methane phosphonates”. Tetrahedron, 67, 3355-3359.

[16] Huong T. D. Nguyen, The T. Nguyen, Phuong T. K. Nguyen, Phuong Hoang Tran, (2017). “A highly active copper-based metal-organicframework catalyst for a friedel–crafts alkylation in the synthesis of bis(indolyl)methanes under ultrasound irradiation”. Arabian Journal of Chemistry.

[17] Shun-Jun Ji, Shun-Yi Wang, Yong Zhang and Teck-Peng Loh, (2004). “Facile synthesis of bis(indolyl)methanes using catalytic amount of iodine at room temperature under solvent-free conditions”. Tetrahedron, 60, 2051–2055.

[18] Siddiqui, Z. N., Tarannum, S., (2013). “Xanthan sulfuric acid: An efficient and biodegradable solid acid catalyst for the synthesis of bis(indolyl)methanes under solvent-free conditions”. Comptes Rendus Chimie, 16, 829–837.

[19] Zolfigola, M. A., Salehi, P., Shiri, M., Tanbakouchian, Z., (2007). “A new catalytic method for the preparation of bis-indolyl and tris-indolylmethanes in aqueous media”. Catalysis Communications, 8, 173–178.

[20] Masoud Mohammadi Zeydi, Nosrat O Allah Mahmoodi, Ghorban Ardeshiri Terogeni, (2017). “Sulfonylbis(1,4-phenylene)bissulfamic acid (SPSA): Introduction of an efficient and reusable catalyst for the synthesis of bis(indolyl)methanes”. Asian Journal of Green Chemistry, 2, 78-88.

[21] Chinnian J. Magesh, Rajagopal Nagarajan, Mani Karthik, Paramasivan T. Perumal, (2004). “Synthesis and characterization of bis(indolyl)methanes, tris(indolyl)methanes and new diindolylcarbazolylmethanes mediated by Zeokarb-225, a novel, recyclable, eco-benign heterogeneous catalyst”. Applied Catalysis A: General, 266, 1–10.

[22] Rekha, M., Manjunath, H. R., Nagaraju, N., (2013). “Mn/Al_2O_3 and Mn/ZrO_2 as selective catalysts for the synthesis of bis(indolyl)methanes: The role of surface acidity and particle morphology”. Journal of Industrial and Engineering Chemistry, 19, 337–346.