



Optimization of the Synthesis of Mikanecic acid diesters with different catalyst using the Taguchi method

R.Nandhikumar^{1-2*}, K.Subramani¹⁻³

¹ R&D centre, Bharathiar University Coimbatore, Tamilnadu, India.

² Global Institute of Engineering and Technology, Tamilnadu, India.

³ PG & Research department of chemistry Islamiah College, vaniyambadi, Tamilnadu, India.

Abstract: This research presents a study of the Taguchi design application to synthesis of a terpenoid, Mikanecic acid diester using different catalyst. The present study includes catalyst, temperature and reaction time as control factors. An orthogonal array of L9 was used and the ANOVA analyses were carried out to identify the significant factors affecting the synthesis of a, Mikanecic acid diester. The yield of synthesis of mikanecic acid diester can be significantly enhanced by optimization of the synthetic process factors. The Taguchi method provided a systematic and efficient methodology for this optimization, with less effort than would be required for most other optimization techniques.

Key Words: Mikanecic acid diester, K₂CO₃, KI, Kaolin clay, optimization, ANOVA, Taguchi method.

1. Introduction

An innovative experimental design methodology based on Taguchi method is employed to synthesize good yield Mikanecic acid diester through Diels Alder type reaction. The Taguchi method is enormously helpful in data analysis and sampling when more than three experimental parameters are to be varied¹. This Technique is based upon a set of orthogonal array methods with optimum settings of each experimental parameter. The purpose of Taguchi analysis²⁻⁸ is to reduce this variability thereby helping to set optimum control or experimental parameters.

Synthetic organic chemistry is the developing, expanding and booming branches of Science. During the past years, synthetic organic research has seen massive growth.⁹⁻¹² Development of latest methods for the synthesis of heterocyclic compound, novel reagents, catalysts, strategies, and transformations is used. In synthetic organic chemistry, the constructions of quaternary carbon center have been one of the demanding and most attractive field due to a number of biologically active natural compounds consisting structural sub-units.¹³⁻¹⁶ Terpenoid dicarboxylic acid and Mikanecic acid have involved our attention due to its special feature of having vinylic quaternary carbon center. In 1936, Manske¹⁷ isolated Mikanecic acid from the alkaloid Mikanoidine obtained by base hydrolysis of *Senecio mikakoides otto*. In literature¹⁸ many research papers have been published based on the synthesis and characterization of Mikanecic acid.¹⁹ Inorganic catalyzed organic reactions are obtaining importance owing to their low-cost nature and special catalytic attributes in various reactions. In this view, our research is focused to develop environmentally benign protocols. Herein, we report, K₂CO₃²⁰⁻²⁵, KI²⁶⁻²⁹ and Kaolin clay³⁰⁻³⁴ catalyzed synthesis of Mikanecic acid diesters results in fairly good yields.

In past years, many researchers developed the Baylis-Hillman reaction. In literature, DABCO³⁵ was used to perform this reaction and it resulted with the slow reaction rates. A Lewis acid (TiCl₄) reaction of acetaldehyde with appropriate acrylates successfully resulted with Baylis-Hillman adducts³⁶⁻³⁸ (**1a-1c**). Then these adducts on treatment with suitable catalysts yielded with Mikaneic acid diesters (**2a-2c**) by Diels-Alder type (i.e. self-dimerization of 1,3-butadiene-2-carboxylate) (Scheme I Table 3). Mikaneic acid diesters on hydrolysis gave Mikaneic acid. (**3**) Furthermore, a large number of experiments have to be accepted out when the number of process factors is large. To explain this problem, the Taguchi method was proposed in the late 1960s. The method, which is one of the partial factorial designs allows one statistically and ideally to obtain similar information to a full-factorial experimental design, but with less experiments. It uses a special design of orthogonal arrays to study the full parameter space. Furthermore, a statistical analysis of variance is performed to see which process factors are statistically significant. Finally, a confirmation testing is conducted to verify the optimal process factors obtained from the Taguchi method.

The Taguchi method has been shown to be a great success in industry for improving the quality of products and processes. The fast growth of interest in the Taguchi method has led to several applications of the method in various fields in a world-wide range of industries and nations. In this work, the Taguchi method was used to optimize the synthetic route factors to improve the yield of Mikaneic acid diester. An L₉ orthogonal array was selected for the experimental layout.

2. Experimental

2.1 Materials and Methods

For this research, the use of chemical, reagents and solvent were bought from the real scientific company, India and used as such. Melting points were found out in an open capillary tube with a Buchi melting point apparatus. Elemental analyses were done by using Perkin-Elmer 240C CHN-analyzer. Perkin Elmer IR spectrophotometer records the ¹H-NMR spectra. This was run in (CDCl₃) solvent at 200 MHz NMR spectrophotometer. In the same way ¹³C-NMR Spectra records the spectrum at 50 MHz.

2.2 Synthesis of Mikaneic Acid

2.2a. K₂CO₃ Catalyst/ KI catalyst/ Kaolin clay catalyst.

The synthetic procedure is very simple method. As shown in Scheme I. 0.01 Mole Baylis-Hillman adducts with the presence of catalyst (K₂CO₃ / KI / Kaolin clay) were refluxed for (1 hr / 1.5 hr / 2 hr) In the presence of (70 °C / 80 °C / 90 °C) temperatures respectively. Then completion of their action (monitored by TLC), common workup and column chromatographic purification (hex/ether, 5:1) gave products, which were characterized by IR, NMR spectral data. The outcomes obtained are very much consistent with literature report. The spectral and analytical data of the compound **2a-c**.

IR (neat): 1713, 1641 cm⁻¹; ¹H-NMR (200 MHz, CDCl₃): δ 1.70-1.91 (1H, m), 2.08-2.15 (1H, m), 2.29-2.43 (3H, m), 2.73-2.91 (1H, m), 3.70 (3H, s), 3.71 (3H, s), 5.11-5.21 (2H, m), 5.79-5.98 (1H, m), 6.98 (1H, m); Anal. Calcd for C₁₂H₁₆O₄: C, 64.26; H, 7.15 %. Found: C, 63.33; H, 6.91%.

Spectral data for Mikaneic acid: IR (KBr): 1690, 1640 cm⁻¹; ¹H-NMR (200 MHz, CDCl₃): δ 1.68-2.81 (6H, m), 5.01-5.30 (1H, m), 5.76-6.03 (1H, m), 6.86 (1H, m), 12.43 (2H, s, br); ¹³C-NMR (50 MHz, CDCl₃): δ 21.59, 29.10, 31.72, 46.52, 114.56, 129.30, 136.78, 140.28, 167.65, 175.22; EI-MS: *m/z* 196 (M⁻); Anal. Calcd for C₁₀H₁₂O₄: C, 61.23; H, 6.13 %. Found: C, 57.49; H, 6.51 %.

Taguchi experimental design

Three process parameters, i.e. catalyst, reflux time and reflux temperature, were selected as controllable factors. Their ranges were chosen based on the conditions often used in industry and reported in the literature. For each process factor, three levels were selected in this study, as shown in Table 1.

Three factors, each at three levels, were considered; therefore, an L₉ orthogonal array with four columns and nine rows was employed. This array has eight degrees of freedom and can handle three-level process factors. Each process factor is assigned to a column, nine process factor combinations being available. Only

nine experiments are required to study the entire parameter space. The experimental layout for the three factors using the L_9 orthogonal array is shown in Table 2.

Tabale.1 Factors and their values investigation

Symbol	Factore	Level 1	Level 2	Level 3
A	Reflux time (hr)	1	1.5	2
B	Catalyst	K ₂ CO ₃	KI	Kaolin
C	Reflux temperature(° C)	70	80	90

Tabale.2 Experimental Layout using an L9 (3) Orthogonal array

Trail no	Level 1	Level 2	Level 3
1	1	1	1
2	1	2	2
3	1	3	3
4	2	1	2
5	2	2	3
6	2	3	1
7	3	1	3
8	3	2	1
9	3	3	2

Tabale.3 Experimental result for the yield of Mikanecic acid diesters

Trail no	Level 1	Level 1	Level 1	Yield(%)
1	1	1	1	55
2	1	2	2	56
3	1	3	3	59
4	2	1	2	50
5	2	2	3	52
6	2	3	1	54
7	3	1	3	52
8	3	2	1	54
9	3	3	2	57

Tabale.4 Mean values for the yield (%) of Mikanecic acid diesters

Factor	Level 1	Level 2	Level 3	Max-Min
A	1.7	-3	0.7	4.7
B	-2.7	-1	1.7	2.7
C	-0.3	-1	-0.7	-0.4

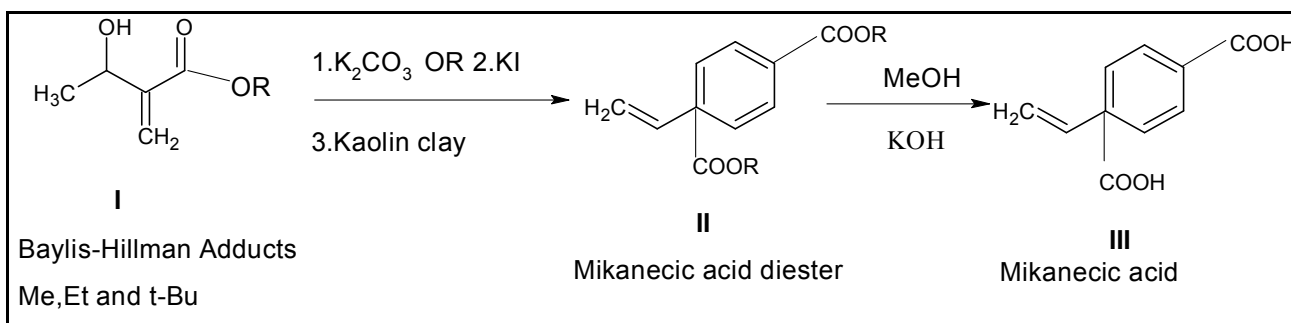
Table.5 Analysis of Variance (ANOVA) of the yield of Mikanecic acid diester

Sources	Some of squares	Degree of freedom	Mean squares	F-test	Table Value 1% level
Factors	SSC=7.5	2	MSC=3.75	MSC/MSE=1.44	(2,6)=10.92
Error	SSE=15.3	6	MSE=2.6	-	-
Total	22.8	8	-	-	-

Determination of quality characteristics

A balance with a precision of 0.0001 g was used to measure the weight of the Mikanecic acid diester sample obtained for each experiment, according to which the yield of Mikanecic acid diester based on Ring formation was determined as the quality characteristic of the Mikanecic acid diester syntheses in the Taguchi method. In addition, the IR spectra of the Mikanecic acid diester samples obtained were recorded on a PerkinElmer Specrum-1000 Fourier transform infrared (FTIR) spectrometer. Samples were prepared as thin films on KBr plates. The melting points of the Mikanecic acid diester samples were measured by a capillary method. The temperature at which a sample began to melt was recorded as the sample melting point.

Scheme: Synthesis of Mikanecic acid diester using different catalysts.



3. Result and Discussion

3.1. Synthesis and Characterization

The synthesis of Mikanecic acid diester from Baylis Hillman adducts using three different catalysts that is two chemical catalysts, K_2CO_3 and KI. Another one is kaolin. In this study first we prepared different Baylis Hillman adducts (**1 a-c**) by using acetaldehyde with different acrylates (Me, Et and t-Bu) in the presence of $TiCl_4$. Chloroform is used as solvent. Further these different Baylis Hillman adducts react with K_2CO_3 , KI and Kaolin to give Mikanecic acid diesters (**2a-c**) and which on hydrolysis gives Mikanecic acid (**3**). (**Scheme I**). All the synthesized compounds were characterized by IR, NMR and mass spectral analysis. In general all the three catalysts were resulted with good yields.

The purpose of the analysis of variance (ANOVA) is to determine which process factors significantly affect the quality characteristic.

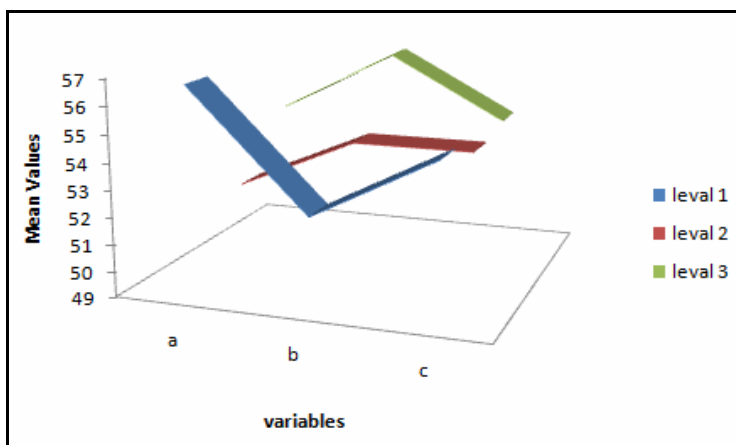


Figure.1 Mean values of synthesis of Mikanecic acid diester.

4. Conclusions

This paper has discussed an application of the Taguchi method for improving the yield of Mikanecic

acid diester. As shown in this study, the Taguchi method provides a systematic and efficient methodology for the optimization of the process factors in Mikanecic acid diester synthesis with far less effort than would be required for most other optimization techniques.

Optimum control parameters were fixed and Synthesis of Diels Alder type reaction was carried out by varying various control factors to obtain good yielding Mikanecic acid diester. Organic chemists working with conducting Mikanecic acid diester synthesis may find this method more useful should they have more than three experimental parameters to vary. Synthesis of Mikanecic acid diester through this innovative method and applying the principles of Taguchi method would ensure less error experimentation and would help to set up optimum control parameters by reducing variation.

Acknowledgment

The authors would like to thank the management, Principal of Global Institution of Engineering and Technology and Bharathiar University, R&D Centre for rendering full support for this work.

References

1. Jiancheng Zhou, Dongfang Wu and Dongsheng Guo, *Published online in Wiley Online Library.*, 14, (2010).
2. Gh. Tahmasebi Pour and S. M. Mirzaee Moghadam, *International Journal of Materials, Mechanics and Manufacturin.*, 2, 1 (2014)
3. Mohsen Jahanshahi, Ghasem Najafpour and Mostafa Rahimnejad, *African Journal of Biotechnology.*, 7 (4), 362-367 (2008).
4. A. Pourjavadi, R. Soleyman, Gh.R. Bardajee and F. Seidi, *Transactions C: Chemistry and Chemical Engineering.*, 17, (2010).
5. Achyut K. Panda, R.K. Singh, *Advanced Chemical Engineering Research.*, 2, 4 (2013).
6. Sameh S. Habib, *International Journal of Scientific Research in Chemical Engineering.*, 1(6), 93-105 (2014).
7. S.N. Paul, Vineet V. Karambelkar, J.D. Ekhe, *Int. Journal of Engineering Research and Applications.* 3, 89-95 (2013).
8. Achyut K. Pandaa, R. K. Singhb, *International Journal of Multidisciplinary and Current*, (2013).
9. K. Reshetova and Y.A Ustynyuk, *Russ.Chem., Bull.*, 53, 335 (2004).
10. G. Zhao, T. Jiang, H. Gao, J. Huang, and D. Sun, *Green Chem.*, 6, 75 (2004).
11. A. Zoupy, A. Petit, F. Hamelin and D. Mathe, *Synthesis.*, 1213 (1998).
12. B.Gangadasu, P.Narender, B. Chinna Raju and V. Jeyathirtha Rao, *Ind. J. Chem.*, 45B, 1259 (2006).
13. S.F Martin *Tetrahedron.* 36, 419 (1980).
14. D. Romo, and A.I. Mayer, *Tetrahedron.*, 47, 9503 (1991).
15. J. Angelo, F. Dumas and A. Guingant *Tetrahedron Asymmetry.*, 3, 459 (1992).
16. B. Das, J. Banerjee and N. Ravindranath, *Tetrahedron.*, 60, 8357 (2004).
17. R.H.F. Manske, *Canad. J. Res.*, 14B, 6 (1936).
18. K. Fuji, *Chem. Rev.*, 93, 2037 (1993).
19. L.K. Sydnes, L.Skattbol and D.G.Lappord *Helv., Chim. Acta.*, 58, 2061 (1975).
20. Swati Ojha, Usha Ameta, Neelam Dhakar and G.L.Talesara, *Ind.J.Chem.*, 46B, 860-865. (2007).
21. V. Singh and S. Batra *Tetrahedron.*, 64, 4511-4574 (2008).
22. Sumathi Bhatia, Sukhdev Singh, Rajesh Kumar, Amit Kumar, Carl.E.Olsen and K. Ashok Prasad, *Ind. J. Chem.*, 52B, 379-386(2013).
23. Urvasi Tiwari, Chetna Ameta, Manish.K.Rawal, Rakshit Ameta and B. Pinki Punjabi, *Ind. J. chem.*, 52B, 42-439(2013).
24. P. R. Kawel, P. R. Deohate and B.N. Berad, *Ind. J. Chem.*, 54B, 833-836(2015).
25. N. Ralph, Salvatore, Cheol. H.wan Yoon and Kyung Woon Jung, *Tetrahedron.*, 57, 7785-7811(2001).
26. Chao-Jun Li, *Chem.Rev.*, 105, 3095-3165 (2005).
27. Saikat Das Sarma, Pallab Pahari, Swapnali Hazarika, Parasa Hazarika, Manash Jyoti Borah and Dilip Konwar, *ARKIVOC.*, 243-263 (2013).
28. Tom. D. Sheppard, *Organic and Biomol.Chem.*, DOI: 10.1039/b818155a (2009).

29. Jun-fa-wei, Li-hui Zhang, Zhan-quo Chen, Xian-ying and Jing-Ling Cao, *Org. Biomol Chem.*, 7 , 3280-3284(2009).
30. M. Balogh and P. Laszolo, *Organic Chem. using Clays.*, 106 2316-2317 (1993).
31. Ponnusamy Shanmugam and Paramasivan Raja Singh, *Synlett.*, 8 , 1314-1316 (2001).
32. Eman. A. Emam, *APRN Jour of Sci and Tech.*, 3 , 4 (2013).
33. Dilipkonwar, K. Pradp, Gogoi, Pranjal Gogoi, GeetikaBorah, Ruby Baruah Neelaksi Hazarika and Rituraj Borgohain , *Ind. J. Chem Tech.*, 15 , 75-78(2008).
34. Gopalpur Nagendrapp, *Applied Clay Sci.*, 53 , 106-138(2011).
35. Deevi Basavaiah, Anumolu Jaganmohan Rao and Tummanapalli Satyanarayana, *Chem.Rev.*, 103 , 811-891(2003).
36. Jeong Beom Park, Seung Ho Ko, Wan Pyo Hong and Kee-Jung Lee, *Angew.chem.Int.Ed.*, 42, 5054-5056(2003).
37. R. Alan, Katritzky, Myong Sang Kim and Khalid Widyan, *ARKIVOC.* 3, 91-101(2008).
38. H. Firouzabadi and M. Jafarpour *J.Iran.Chem.Soc.*, 5 , 159-183 (2008).
