

**Keywords**

Diels-Alder Reaction,
Ionic Liquid,
Solid Supports,
Microwave, 1,3-Butadiene

Received: March 26, 2015

Revised: April 14, 2015

Accepted: April 15, 2015

Diels-Alder Reactions of 1,3-Butadiene Assisted by Solid Supports and Microwave Irradiation: A Green Protocol

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Citation

Annamalai Rajendran, Ganesan Vinoth Kumar. Diels-Alder Reactions of 1,3-Butadiene Assisted by Solid Supports and Microwave Irradiation: A Green Protocol. *AASCIT Journal of Chemistry*. Vol. 2, No. 3, 2015, pp. 61-66.

Abstract

The microwave-assisted organic reactions in ionic liquids are proved to be sustainable technology with higher yields in short reaction time. Thus, the principles of green chemistry such as short reaction time, variety of reactions while avoiding exposure of hazardous chemicals and maximum utilization of energy are achieved by utilizing microwave technology in green synthetic processes; In addition to microwave energy, solid supports are also have occupied a significant role for boosting the green chemistry principles. These features enable microwave assisted synthesis as an effective and convenient tool for commercial as well as academic research. The main objective of present study explores utility of microwave assisted green mediated synthesis of 4-cyclohexene-1,2-dicarboxylic anhydride and 4-cyclohexene-1,2-dicarboxylic acid from Diels-Alder reactions of 1,3-butadiene with maleic anhydride and maleic acid respectively in the presence of solid supports. Diels-Alder reactions were performed using microwave assisted synthesis on a Biotage microwave reactor, at 60°C power level and fixed time period of, as well as by conventional method of synthesis at room temperature; All the reactions were conducted extensively to obtain excellent yields of products which was separated out using typical literature methodologies. The Diels-Alder cycloadducts were purified by recrystallization using suitable petroleum ether. All the reactions of microwave assisted and conventional method of syntheses were monitored by GC-MS spectrometer. In this paper we have established the methods for synthesis of 4-cyclohexene-1,2-dicarboxylic anhydride and 4-cyclohexene-1,2-dicarboxylic acid by microwave assisted synthesis with short time of synthesis and practical green chemistry approach.

1. Introduction

Due to the exclusive solvent properties such as high thermal stability and insignificant vapor pressure, ionic liquids have emerged outstandingly as non-aqueous green reaction media and an alternative to organic solvents for the past 15 years [1-3]. The field of synthetic organic chemistry mainly concentrates on atom efficiency in order to avoid loss of molecular energies in the form of undesirable side reaction products. In other words, all the reactants should be converted to main products in a easier way with short reaction duration [4-7]. Green chemistry approaches are suitable methods for fulfilling these criteria. Synthesizing organic compounds using Diels-Alder reaction is one of the best tools to attain these expectations. In recent years, the trend have been modified towards the non-conventional, pollution less and environmentally benign processes of syntheses

[8,9]. That's why, the ionic liquids have been widely used in the organic synthetic field. Although whatever may be the type of ionic liquid utilized in synthetic processes, using non-coordinating anions as the negative counterparts (AlCl_4^- , BF_4^- , PF_6^- and SbF_6^-) instead of using coordinating anions like Cl^- also have given additional significant contributions in enhancing the rates and yield of chemical reactions. [10] In order to accelerate the rate remarkably and to increase yield, the first ever microwave assisted synthesis was carried out by Gedye and Giguere in 1989 in a household microwave oven[11]. After that, the field of microwave assisted synthesis had been developed drastically from household microwave oven to specially made microwave reactor synthesis [12-24]. Now a days, the utilization of microwave technology on organic synthesis has been applied for the multistep or single step reaction processes extensively in academic and commercial research fields [25-27].

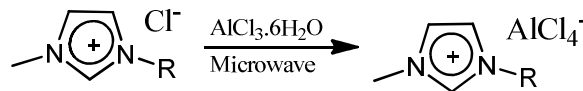
Solid supports have been widely used in most of the organic synthetic reactions in order to obtain high yields in relatively short reaction time[28]. These efficient solid supports have been extensively applied in green and microwave assisted organic syntheses, which acted as a boost to the organic reactions in the view of reaction rates. The present study in our laboratory provides the combined effects of microwave energy, solid supports in 3-methyl-1-octyl-imidazolium tetrachloroaluminate, [MOIM] AlCl_4 ionic liquid. This chloroaluminate ionic liquid was employed as reaction media for the reactions of 1,3-butadiene with maleic anhydride and maleic acid. The application of this chloroaluminate ionic liquid was employed in the Diels-Alder reactions for the first time around the year 2000[29]. A versatile, fast and efficient green microwave-assisted work-up procedure was described for the Diels-Alder reactions of 1,3-butadiene with maleic anhydride and maleic acid. In this procedure all reactions were proceeded smoothly and efficiently.

2. Materials and Methods

2.1. Chemicals and Instruments Required

^1H and ^{13}C NMR (300 MHz) spectra analyses were carried out on Bruker AVANCE spectrometer (Bruker BioSpin AG, Fällanden, Switzerland; 300 MHz) using TMS as internal standard. FT-Infrared spectra were recorded on a Perkin Elmer (Model-Frontier) spectrophotometer (Waltham, MA, USA). Electrospray Ionization Mass Spectra (GC-ESI-MS) were recorded on a Thermo LCQ Deca XP MAX GC – MS instrument equipped with electrospray (ESI). Melting point was recorded on a Thermo Cal / μ ThermoCal₁₀ automatic capillary point apparatus. Diels-Alder reactants (Scheme 2 and 3) were purchased from Aldrich Chemical Company Inc. All other reagents were of analytical grade from commercial sources. The ionic liquid, 3-methyl-1-octyl-imidazolium tetrachloroaluminate, [MOIM] AlCl_4 was prepared (Scheme 1) from aluminium chloride hexahydrate and 3-methyl 1-octyl

imidazolium chloride followed by the procedure provided in the literature[30]. A microwave reactor (Biotage, Power range: 0-300 W at 2.45 MHz) was used for all the microwave-assisted Diels-Alder reactions to be performed.



Where R = Octyl

Scheme 1. Synthesis of ionic liquid [MOIM] AlCl_4 .

2.2. Experimental Section

General procedure for synthesis of the Diels-Alder adducts a and b (Scheme 2 and 3) in conventional method

The ionic liquid [MOIM] AlCl_4 (2 mL), 2 mmol of corresponding dienophile and an appropriate amount of solid support were mixed in a 25 mL round bottomed flask and then the vial was pressurized with 1,3-butadiene at room temperature. The intake of 1,3-butadiene(1) by the reaction mixture was monitored by the decrease of the vial's pressure. The reaction mixture was subjected to magnetic stirring in the rate of 1000 rpm, since the mass transfer between gaseous and liquid phases is an important parameter in this set-up. Because, in absence of magnetic stirring the consumption of 1,3-butadiene is completely stopped. The progress for all reactions were determined by analyzing the organic phase using GC-MS spectrometer. After completion of the reaction, the handlings and separations of the phases were performed under air at 0 °C. After solvent extraction with diethyl ether (5 X 6 mL), the crystalline Diels-Alder adduct was purified by recrystallization using petroleum ether. The purified product was characterized by ^1H NMR, ^{13}C NMR, IR and GC-MS measurements.

General procedure for synthesis of the Diels-Alder adduct a and b in microwave method

The ionic liquid [MOIM] AlCl_4 (2 mL), 2 mmol of dienophile, 2.2 mmol of liquid 1,3-butadiene and an appropriate amount of solid support were mixed in a 20 mL microwave vial. The mw-vial containing the reaction mixture was adopted into Biotage microwave reactor. After 15 s of initial pre mixing the content present in the mw-vial was irradiated to 60 °C for one minute with 15 s of initial mixing. The progress of the reaction was determined by GC-MS instrument. The crystalline product was extracted and purified as stated above (Section 2.1). Finally, the product was characterized by ^1H NMR, ^{13}C NMR, IR and GCMS measurements.

Spectral data of 4-cyclohexene -1,2 -dicarboxylic anhydride (a)

Colorless crystalline solid, mp 102 °C. ^1H -NMR (300 MHz, Acetone- d_6 , ppm, δ) = 2.530 (4H, dd, 2- CH_2), 3.55 (2H, t, 2-CH), 5.950 (2H, t, 2-CH, vinyl).

^{13}C -NMR (300 MHz, CDCl_3 , ppm, δ) = 28.230, 42.128, 123.114, 172.223.

ESI-MS: m/z = 153.0546 calculated for $[\text{M}+\text{H}]^+$; found

152.6521

IR (KBr, cm^{-1}): at 2950, 2900, 1780, 940.

Spectral data of 4-cyclohexene-1,2-dicarboxylic acid (b)

Colorless crystalline solid, mp 164°C. 1H -NMR (300 MHz, Acetone- d_6 , ppm, δ) = 2.413 (2H, m, 2- CH_2), 2.530 (2H, m, 2- CH_2), 3.05 (2H, dt, 2-CH), 5.692 (2H, t, 2-CH, vinyl), 10.513 (2H, s, 2-COOH)

^{13}C -NMR (300 MHz, $CDCl_3$, ppm, δ) = 26.038, 39.024, 125.527, 174.130.

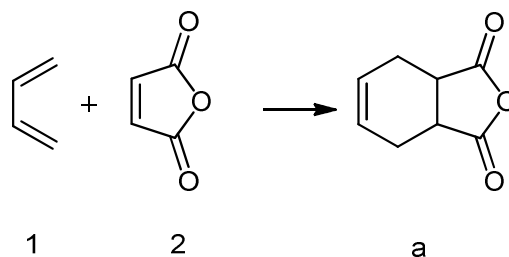
ESI-MS: m/z = 171.0651 calculated for $[M+H]^+$; found 170.6125.

IR (NaCl, cm^{-1}): at 3000, 2900, 1700, 1440, 1260, 960.

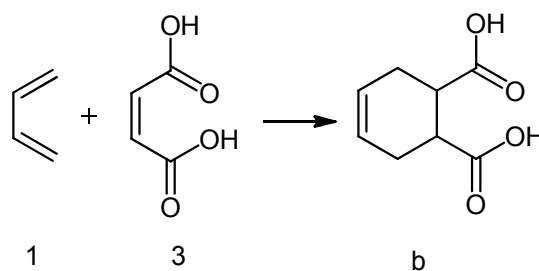
3. Results and Discussion

3.1. Solid supported Diels-Alder Reactions in Ionic Liquid

The ionic liquid $[MOIM]AlCl_4$ readily dissolves 1,3-butadiene **1**, maleic anhydride **2**, maleic acid **3** and solid supports on simple stirring the reaction mixture. Hence, two types of Diels-Alder reactions were investigated (Scheme 2 and 3) using this solvent media. Using the 1,3-butadiene and a set of two dienophiles maleic anhydride and maleic acid had been carried out at various reaction conditions. In all types of reactions solid supports were applied for investigating about the improvement in rate and yield of reactions. The solid supports utilized for the analyses are $LiNTf_2$, $Sc(OTf)_3$, $Y(OTf)_3$, K-10, SiO_2-60 and Al_2O_3 . All the microwave assisted reactions were carried out at 60°C and conventional reactions were at 25°C. The excellent ability of these solid supports were observed although there was a relatively some variations in their efficiency in the view of reaction time and yield (Table 1 and 3). Table 1 depicts the time courses of the Diels-Alder reactions between 1,3-butadiene and maleic anhydride and table 3 describes reaction between 1,3-butadiene and maleic acid in 2 mL of $[MOIM]AlCl_4$ mixed with 0.750 g of solid support, by using microwave irradiation (60°C) and conventional heating (25°C). The well designed solvent medium have achieved good to excellent conversions to synthesize 4-cyclohexene-1,2-dicarboxylic anhydride **a** and 4-cyclohexene-1,2-dicarboxylic acid **b** in both cases, 85-97% in conventional method but taking 1.30-6.00 h of duration for the completion of both the reactions and 80-96% under MW irradiation but within 45-120 s only (Table 1 and 3). From these results it can be observed that $LiNTf_2$ have very good tendency in enhancing reaction rates. $Sc(OTf)_3$ and $Y(OTf)_3$ are also have almost equivalent efficiency to $LiNTf_2$ providing good conversion rates. Tables 2 and 4 depict the excellent potential of $LiNTf_2$ at various load study of reactions. Best tendency of activity of this solid support were observed while using 0.750 g and 1.00 g of solid support.



Scheme 2. Synthesis of 4-cyclohexene-1,2-dicarboxylic anhydride



Scheme 3. 4-cyclohexene-1,2-dicarboxylic acid

3.2. The Role of Solid Materials in the Generation of the Diels-Alder Products

Although the exact mechanism of catalytic activity of metal triflates and other solid supports are not well known, it is considered that the solid supports may form a reactive intermediate complexes with the dienophiles maleic anhydride and maleic acid leading to enhance the rates of the reactions with 1,3-butadiene. During the intermediate complex formation the energy of the dienophiles to react with diene may be increased enormously, which in turn, favouring the reactions in both the microwave and conventional methods [31].

3.3. Reaction Parameters for Microwave-Assisted Synthesis in Ionic Liquid

Tables 2 and 4 designate the observed improvements in the rate of solid supported Diels-Alder reactions for the synthesis of **a** and **b** as result of loading microwave energy into the reaction vial through Biotage microwave initiator plus synthesizer. The temperature was pre-programmed as 60°C to complete the reactions within 45 s for scheme 1 and 120 s for scheme 2 reactions. Comparing to conventional stirring method which occurs at maximum 6 h duration, the microwave reactions are completed within few seconds (Tables 1-4). It can be observed that the role of solid supports have occupied major role for the synthesis of **a** and **b** in both the methodologies.

3.4. Separation of Diels-Alder Adducts from Ionic Liquid

For microwave assisted synthesis, after completion of the reactions, the cyclo addition adducts were isolated from ionic liquid after allowing the reaction to room temperature through solvent extraction. In conventional method of

synthesizing **a** and **b**, the 1,3-butadiene had been used as a pure gaseous substance in our laboratory. After completion of the reactions in this method, the unreacted gaseous 1,3-butadiene substrate should not be allowed to eliminate through diffusion in the air like a normal gaseous phase reactant. Because it is well known that 1,3-butadiene is a carcinogenic chemical. Henceforth utmost care to be taken before eliminating this substance. DNA adducts are formed by the BD (butadiene) metabolites which are known as primary root cause of carcinogenic process.[32] Therefore sufficient precautions should be taken before handling this gaseous substance. At 0 °C the unreacted gaseous butadiene was eliminated through outlet and was collected in a small container having stopcock. After finishing of this process, the Diels-Alder adducts **a** and **b** were separated and purified as stated in the experimental section above. In microwave method, as liquid butadiene was used, the separation

processes were done as usual work-up process by solvent extraction using petroleum ether.

3.5. Recycling and Applications of Ionic Liquid

In our investigation, although all the solid supports have outstanding performance, among them LiNTf₂ found to have the superior tendency towards the synthesis of **a** and **b**. Hence, the characteristics of this solid support was analyzed by subjecting it to the recycling process along with ionic liquid [MOIM]AlCl₄ in microwave and conventional methods. The results of this novel green medium have shown in Fig. 1 and Fig. 2. Up to the fifth cycle (A-E) only around 10% of yield was lost. These results reveal that this ionic liquid-solid support combination is really a sustainable source of energy.

Table 1. Diels-Alder reaction between 1,3-butadiene and maleic anhydride using various solid supports.

Entry	Support ^a	Conventional ^b		Micro wave ^c	
		Time,h	Yield, % ^d	Time,s	Yield, % ^e
1	LiNTf ₂	1.15	97	45	96
2	Sc(OTf) ₃	1.45	95	45	94
3	Y(OTf) ₃	2.45	90	45	92
4	K-10 ^f	3.30	87	45	87
5	SiO ₂ -60 ^g	4.00	86	45	83
6	Al ₂ O ₃ ^h	6.00	85	45	80

Reaction conditions: ^aAmount of Solid Supports = 0.750 g, ^bTemperature = 25°C, ^cTemperature=60°C, ^{d,e}Isolated yield, ^fK-10 montmorillonite, ^gSilica gel 60 (0.040-0.063 mm), ^hActivated, neutral, Brockmann I (150 mesh) aluminium oxide.

Table 2. Diels-Alder reaction between 1,3-butadiene and maleic anhydride using LiNTf₂.

Entry	Amount of LiNTf ₂ , g	Conventional ^a		Micro wave ^b	
		Time, h	Yield, % ^c	Time, s	Yield, % ^d
1	0.050	1.15	35	45	55
2	0.125	1.15	72	45	84
3	0.250	1.15	78	45	90
4	0.500	1.15	86	45	92
5	0.750	1.15	97	45	96
6	1.000	1.15	97	45	96

Reaction conditions: ^aTemperature = 25°C, ^bTemperature=60°C, ^{c,d}Isolated yield.

Table 3. Diels-Alder reaction between 1,3-butadiene and maleic acid using various solid supports.

Entry	Support ^a	Conventional ^b		Microwave ^c	
		Time,h	Yield,% ^d	Time,s	Yield,% ^e
1	LiNTf ₂	1.30	95	120	97
2	Sc(OTf) ₃	2.00	94	120	93
3	Y(OTf) ₃	3.00	94	120	92
4	K-10 ^f	4.00	85	120	85
5	SiO ₂ -60 ^g	4.30	86	120	83
6	Al ₂ O ₃ ^h	5.30	87	120	86

Reaction conditions: ^{a-h}As provided in Table 1.

Table 4. Diels-Alder reaction between 1,3-butadiene and maleic acid using LiNTf₂.

Entry	Amount of LiNTf ₂ , g	Conventional ^a		Microwave ^b	
		Time, h	Yield, % ^c	Time, s	Yield, % ^d
1	0.050	1.30	29	120	48
2	0.125	1.30	75	120	81
3	0.250	1.30	80	120	92
4	0.500	1.30	86	120	94
5	0.750	1.30	95	120	97
6	1.000	1.30	95	120	97

Reaction conditions: ^{a-d}As provided in Table 2.

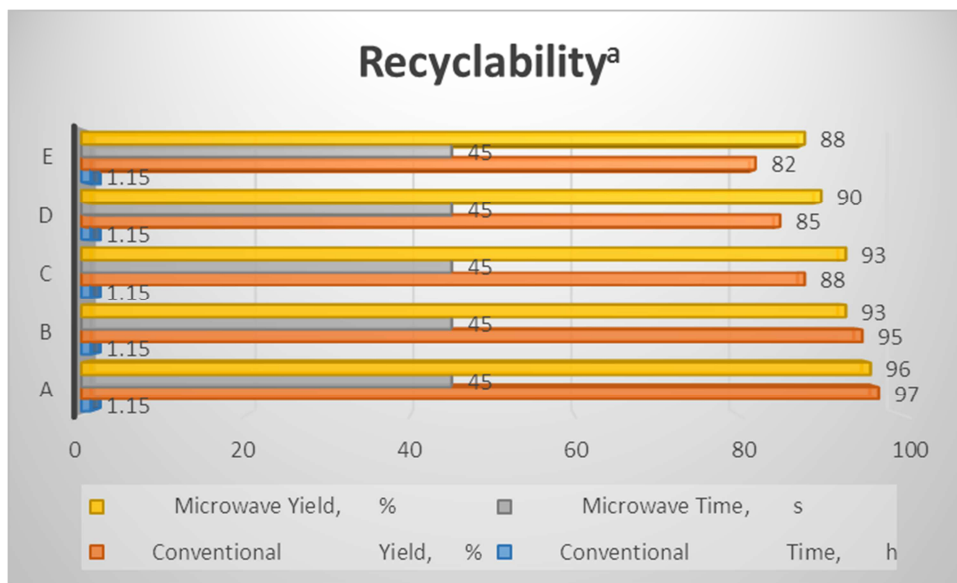


Fig. 1. Recyclability of the system, 2 mL of ionic liquid [MOIM] AlCl₄ mixed with 0.750 g of LiNTf₂ for the reaction between 1,3-butadiene and maleic anhydride in conventional and microwave irradiation methods.

^aReaction conditions: 2 mL of [MOIM] AlCl₄, 0.750 g of LiNTf₂, temperature = 25 °C (Conventional), time = 1.15 h (Conventional), temperature = 60 °C (mw), time = 45 s (mw), isolated yield, Note: A, B, C, D, E are notations for recycling processes.

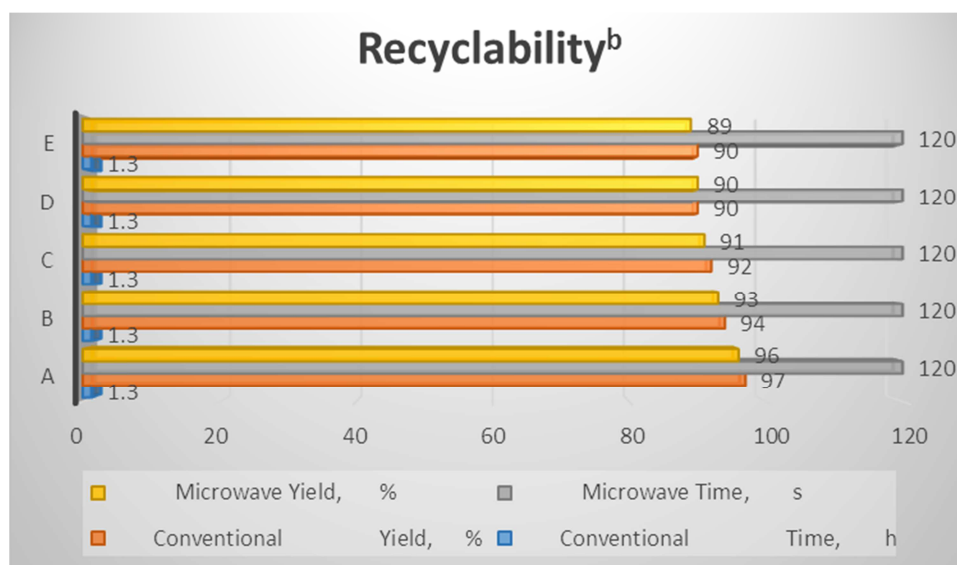


Fig. 2. Recyclability of the system, 2 mL of ionic liquid [MOIM] AlCl₄ mixed with 0.750 g of LiNTf₂ for the reaction between 1,3-butadiene and maleic acid in conventional and microwave irradiation methods.

^bReaction conditions: As stated above (Fig. 1).

4. Conclusion

Within this study, novel, sustainable green medium for the Diels-Alder reactions between 1,3-butadiene with maleic anhydride and maleic acid in conventional and microwave irradiation methods have been established. Changes in the composition of solid supports in [MOIM]AlCl₄ ionic liquid, demonstrated dramatic effect on the Diels-Alder reaction of 1,3-butadiene with maleic anhydride and maleic acid and the optimum yields were obtained while using 0.750 g of LiNTf₂ in both the methods. Thus, the powerful starting materials have been designed for the synthesis of 4-cyclohexene-1,2-dicarboxylic anhydride and 4-cyclohexene-1,2-dicarboxylic acid through Diels-Alder reactions. In order to obtain high yields in a fraction time duration, efforts could be made drastically through microwave technology and using suitable solid supports for synthesizing organic compounds in ionic liquids as an environmentally-friendly manner.

Acknowledgement

The authors are thankful to the Bharathiar University, Coimbatore and Sir Theagaraya College, Chennai, India for their valuable support to carry out this work successfully.

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