

## A Green, Sustainable Diels-Alder Protocol for the Synthesis of Tetrahydro-1H-isoindole-1,3(2H)-dione Catalyzed by Chiral Ionic Liquid.

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### Abstract

A convenient procedure has been established for the preparation of tetrahydro-1H-isoindole-1,3(2H)-dione (Diels-Alder adduct) using maleimide catalyzed by imidazole based achiral and chiral ionic liquid, under solvent free environments. Achiral and chiral ionic liquids are used as a solvent and a catalyst. Operational simplicity, reusable catalyst, no tedious work up, environment friendly and high yields are some of the key features of the protocol.

**Keywords:** chiral ionic liquid, chiral HPLC, organocatalyst, green chemistry, environment friendly.

### 1. Introduction

Tetrahydro-1H-isoindole-1,3(2H)-dione have been widely used as a versatile synthetic intermediate for the preparation of various bioactive compounds [1]. Conventionally, tetrahydro-1H-isoindole-1,3(2H)-dione derivatives have been synthesized using Diels-Alder reaction, which has been one of the most versatile reaction used for C-C bond formation [2-4]. In the past few decades, Diels-Alder reaction between isoprene and aryl maleimides has been carried out in the presence of chiral host in water suspension medium [1], activated chiral oxazaborolidines [5], DDQ [6], AlCl<sub>3</sub> + THF [7] and homochiral metal organic framework [8]. The aforementioned protocols suffer from drawbacks such as tedious methods, moderate yields, use of expensive and toxic reagents, catalysts and solvents, with longer reaction time. Hence, there is a constant need to develop a convenient, green and sustainable protocol for the preparation of tetrahydro-1H-isoindole-1,3(2H)-dione.

The use of a chiral ionic liquid (CIL) and an achiral ionic liquid (AIL) in organic reactions have attracted considerable interest, as a green solvent or an organocatalyst [9-10]. CIL and AIL has highly desirable solvent properties. The “green” and “designer” properties have made chiral and achiral ionic liquids attractive alternatives to conventional solvents used for various organic transformation [11].

Previously, imidazolium based “CIL, 1-butyl-3-methylimidazolium (T-4)-bis[(2S)-2-(hydroxy-□O)propanoato-□O]borate (BMIm<sup>+</sup>BLLB<sup>-</sup>)” [12-13] and “AIL, 1-butyl-3-methylimidazolium chloride (BMIm<sup>+</sup>Cl<sup>-</sup>)” [14] was employed successfully for the preparation of “tetrahydro-4,9[1',2']-benzeno-1H-benz[f]isoindole-1,3(2H)-diones” [13-15]. We envisioned the use of chiral ionic liquid BMIm<sup>+</sup>BLLB<sup>-</sup> for the preparation of tetrahydro-1H-isoindole-1,3(2H)-dione under solvent free conditions. To the best of our knowledge, preparation of racemic and enantiomerically enriched tetrahydro-1H-isoindole-1,3(2H)-dione using achiral and chiral ionic liquids under solvent and metal free conditions has not been explored so far.

### 2. Material and methods

#### 2.1 General

“All other reagents and solvents are of commercial quality and are used as supplied without further purification, unless otherwise noted. Not all melting points are corrected. The temperatures are recorded in °C. The infrared spectra were recorded on a Shimadzu FTIR-4200 spectrometer. The <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on a Bruker ACF300 spectrometer (300 MHz). Chemical changes have been reported in parts per million (ppm). The residual solvent peak was used as an

internal reference. purity was determined by HPLC analysis in UV1000 HPLC units from the Fisher thermo spectra system by using Chiralpak AD/ Kromasil-5-CelluCoat (4.6 mm i.d. x 250 mm) with solvent mixture of hexane/2-propanol 97/03; flow rate 2.0 ml/min; temp 19 °C; detection UV 258/335 nm.” [13-15].

## 2.2 Procedures and methods

**Representative Procedure for Enantioselective Diels–Alder between isoprene and aryl maleimides in CIL (BMIm<sup>+</sup>BLLB<sup>-</sup>) (4a-4d):** To a solution of CIL (BMIm<sup>+</sup>BLLB<sup>-</sup>) (1g; 3.0 mmol), *N*-phenyl maleimide (0.173g; 1.0 mmol) was added and the mixture was stirred at RT for 10 min. 2-methyl-1, 3-butadiene (0.136g; 2.0 mmol) was added to the above reaction mixture and the reaction mixture was permitted to stir under dry conditions for suitable time (**Table 1.1**). The reaction was monitored by TLC, after completion the reaction mixture was poured into water; the product was filtered off and dried to furnish a colorless product.

**2.2.1 5-methyl-2-phenyl-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione (4a):** Yield: 0.088g (93.62%), Mp: 94-96 °C, Optical rotation:  $[\alpha]_D^{19} -21.25$  (c 0.86, CHCl<sub>3</sub>), IR (KBr, cm<sup>-1</sup>): 3104, 3012, 3034, 3066, 2998, 2943, 2912, 2896, 2846, 1704, 1593, 1500, 1395, 1317, 1202, 1154. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>, ppm): 1.779(s, 3H), 2.245-2.353(m, 2H), 2.567(m, 2H), 3.180-3.301(m, 2H), 5.614-5.641(m, 1H), 7.210-7.268(m, 2H), 7.352-7.487(m, 3H), <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): 23.44, 24.51, 28.90, 39.26, 39.69, 120.16, 126.40, 128.51, 129.08, 132.11, 136.56, 179.15, 179.37.

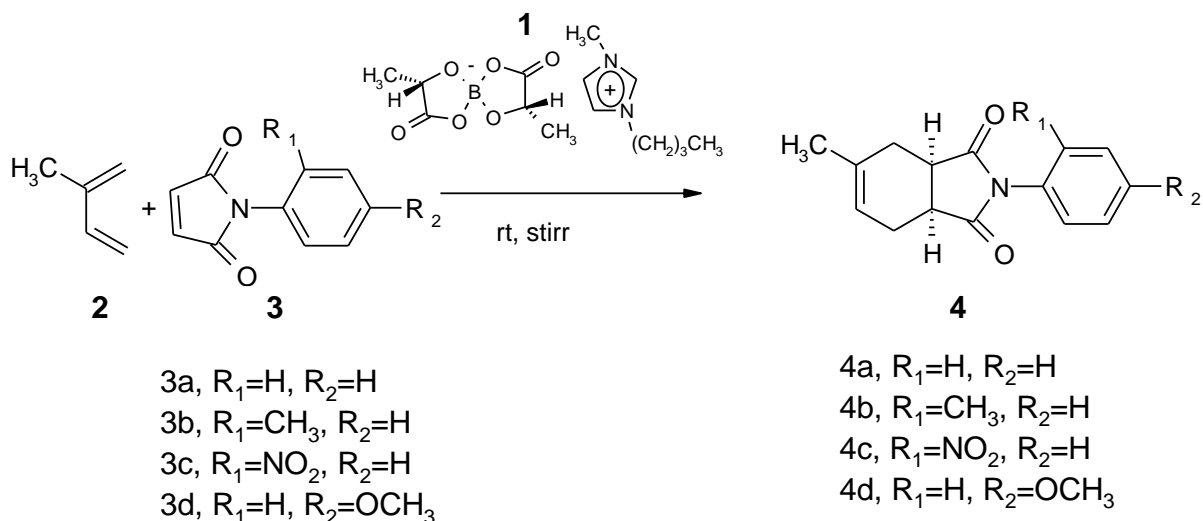
**2.2.2 5-methyl-2-(*o*-tolyl)-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione (4b):** Yield: 0.087g (93.83%), Mp: 143-145 °C, Optical rotation:  $[\alpha]_D^{19} -5.34$  (c 1.03, CHCl<sub>3</sub>) IR (KBr, cm<sup>-1</sup>): 3057, 3055, 2949, 2849, 1704, 1496, 1392, 1312, 1205, 1153. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>, ppm): 1.788(s, 3H), 2.031(s, 3H), 2.241-2.347(m, 2H), 2.585-2.723(m, 2H), 3.258-3.315(m, 2H), 5.659(m, 1H), 7.044(d, 1H, 6.9Hz), 7.236-7.353(m, 3H), <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): 17.71, 23.46, 24.51, 28.93, 39.42, 39.63, 120.18, 120.66, 126.88, 129.40, 131.42, 135.73, 137.00, 179.13, 179.39.

**2.2.3 5-methyl-2-(*o*-nitrophenyl)-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione (4c):** Yield: 0.085g (95.28%), Mp: 98-100 °C, Optical rotation:  $[\alpha]_D^{19} -24.49$  (c 1.04, CHCl<sub>3</sub>), IR (KBr, cm<sup>-1</sup>): 3113, 3071, 3033, 2958, 2903, 2848, 1708, 1607, 1583, 1525, 1391, 1344, 1317, 1263, 1195, 1152. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>, ppm): 1.783(s, 3H), 2.322-2.349(m, 2H), 2.532-2.675(m, 2H), 3.231-3.323(m, 2H), 5.641(m, 1H), 7.268-7.390(m, 1H), 7.516-7.616(m, 1H), 7.702(ddd, 1H, J=1.4Hz, 1.5Hz, 7.5Hz), 8.107-8.333(m, 1H), <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): 23.47, 24.47, 28.81, 39.68, 39.79, 40.14, 120.12, 124.29, 125.76, 126.79, 129.86, 134.16, 136.65, 137.55, 178.38, 178.58.

**2.2.4 5-methyl-2-(*p*-methoxyphenyl)-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione (4d):** Yield: 0.085 g (93.63%), Mp: 85-87 °C, Optical rotation:  $[\alpha]_D^{19} -3.88$  (c 1.44, CHCl<sub>3</sub>), IR (KBr, cm<sup>-1</sup>): 3015, 2943, 2840, 1704, 1609, 1588, 1513, 1403, 1312, 1300, 1254, 1208, 1030. <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>, ppm): 1.774(s, 3H), 2.268-2.341(m, 2H), 2.557-2.629(m, 2H), 3.190-3.251(m, 2H), 3.819(s, 3H), 5.606-5.634(m, 1H) 6.945(m, 2H), 7.109(m, 2H), <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): 23.44, 24.51, 28.90, 39.19, 39.61, 55.46, 114.41, 120.15, 124.75, 127.60, 136.55, 159.44, 179.39, 179.61

## 3. Results and discussion

In the present work, we wish to report our findings on imidazole based chiral ionic liquid, “1-butyl-3-methylimidazolium (T-4)-bis[(2*S*)-2-(hydroxy-□O) propanoato-□O]borate (BMIm<sup>+</sup>BLLB<sup>-</sup>)”<sup>12</sup> mediated Diels-Alder reaction between aryl maleimides and isoprene avoiding the use of acid or metal catalysts and environmentally hostile hazardous organic solvents (**Scheme 1**). Furthermore, a small amount of chiral ionic liquid can mediate the reaction in less time.



**Scheme 1:** D-A reaction between isoprene and aryl maleimides in CIL (**BMIm<sup>+</sup>BLLB<sup>-</sup>**).

In a first set of experiments, **BMIm<sup>+</sup>BLLB<sup>-</sup>** (3.0 mmol) was added to *N*-phenyl maleimide (1.0 mmol); the reaction mixture was permitted to stir for 10 minutes. This was followed by addition of 2-methyl-1, 3-butadiene (2.0 mmol) and the reaction mixture was vigorously stirred for appropriate time (**as mentioned in Table 1.1**). To our satisfaction, the reaction proceeded rapidly furnishing tetrahydro-1H-isoin-dole-1,3(2H)-dione in good yields, the structure of which was confirmed using 1D, 2D NMR and mass. On completion of the reaction, the chiral ionic liquid was recovered easily from the reaction mixture by simple filtration of the products and evaporation of the aqueous solution. The catalytic potentiality of **BMIm<sup>+</sup>BLLB<sup>-</sup>** was investigated for carrying out Diels-Alder reaction with various substituted maleimides (**Table 1.1**). To our delight, the chiral ionic liquid was found suitable to be used up to three catalytic cycle and after that it resulted in incomplete conversion to product even after 24 hours.

Accordingly, a series of tetrahydro-1H-isoin-dole-1,3(2H)-dione derivatives were prepared using the present synthetic methodology. All the products were isolated as an enantiomeric mixture. The enantiomeric excesses of tetrahydro-1H-isoin-dole-1,3(2H)-dione derivatives were determined by HPLC using a chiral stationary phase on column Chiralpak AD (4.6 mm i.d. x 250 mm) and Kromasil-5-CelluCoat (4.6 mm i.d. x 250 mm)

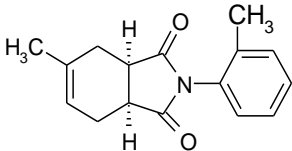
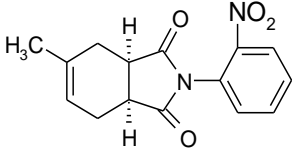
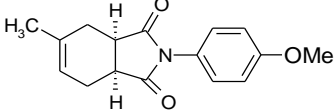
**Table 1.1** Yields, melting points and time of **4a-4d**.

Compound	R <sub>1</sub>	R <sub>2</sub>	Time (min.)	Yield %	Mp °C
<b>4a</b>	H	H	55	93.62	94-96
<b>4b</b>	CH <sub>3</sub>	H	50	93.83	143-145
<b>4c</b>	NO <sub>2</sub>	H	60	95.28	98-100
<b>4d</b>	H	OCH <sub>3</sub>	45	93.63	85-87

The enantiomeric excesses of enantiomerically enriched Diels-Alder adducts **4a-4d** obtained by reaction of isoprene (**2**) with maleimides (**3**) catalyzed by **BMIm<sup>+</sup>BLLB<sup>-</sup>** (**1**) are shown in **Table 1.2**.

**Table 1.2** % ee data of optically active Diels-Alder adducts **4a-4d** using IL

Compound	Structure	% ee
<b>4a</b>		<b>02</b>

<b>4b</b>		<b>11</b>
<b>4c</b>		<b>03</b>
<b>4d</b>		<b>14</b>

Considerably low enantioselectivity was observed in all cases of Diels-Alder adducts **4a-4d**. The same reaction was also attempted by adding ytterbium triflate to the CIL, but there was no improvement in the enantioselectivity. It can be concluded from results that the lactic borate, binds mainly to the dienophile component and hence some facial selectivity was observed. It does not appear to bind to the diene and the dienophile component simultaneously hence stereo-discrimination was rather low in most cases. Thus, the borate based ionic liquid needs to be further explored for chiral application.

#### 4. Conclusion

In summary, a mild and sustainable protocol has been developed for preparation of tetrahydro-1H-isoindole-1,3(2H)-dione derivatives using a convenient and a recyclable chiral ionic liquid. The simple experimental procedure, use of convenient catalytic system, fast reaction, easy product separation and reusability of the catalyst makes this protocol superior to the existing methodologies in this area.

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#### 6. References

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