



SYNTHESIS OF ISOXAZOLIDINE VIA 1,3-DIPOLAR CYCLOADDITION OF N-4-TERT-BENZYLIDENE NITRONE AND MALEIMIDE IN IMIDAZOLIUM-BASED IONIC LIQUIDS

(Sintesis Sebatian Isoxazolidina Melalui Tindakbalas 1,3-Dwikutub Pensiklotambahan
N-4-Tetra-Benzilidina Nitron dan Maleimida dalam Cecair Ionik Berasaskan Imidazolium)

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Abstract

The development of environmentally friendly methodologies for pericyclic reactions such as Diels Alder reaction is astonishing. Nevertheless, this is still scarce for the rest of pericyclic reactions. In this work, diastereoisomeric cycloadducts were formed via 1,3-dipolar cycloaddition between *N*-4-Tert-Benzylidene nitron and maleimide in imidazolium-based ionic liquids (ILs) at 25 °C. Cycloaddition between nitron **1** and maleimide **2** give diastereoisomeric adducts with 1:1 and 1:2 *trans/cis* ratio in two ionic liquids, [Bmim][PF₆] and [Bmim][BF₄], respectively. [Bmim][PF₆] give the desired cycloadducts in 43% yield compared to only 18% yield in [Bmim][BF₄]. In comparison, when the similar reaction was conducted in chloroform, the diastereoisomeric mixture favoured *trans* isomer in 6:0.2 ratio. We reasoned that the repulsive van der Waals interactions favouring *exo* transition state was assisted by imidazolium ionic liquids. Thus, ILs have shown great potential as second reaction media in dipolar cycloaddition reactions.

Keywords: pericyclic reactions, 1,3-dipolar cycloaddition, imidazolium ionic liquids

Abstrak

Tindak balas Diels Alder merupakan contoh tindak balas perisiklik yang mesra alam serta mendapat perhatian ramai. Namun begitu, contoh lain tindak balas perisiklik masih lagi terhad. Melalui kajian ini, tindak balas 1,3-dwikutub pensiklotambahan di antara *N*-4-Tetra-Benzilidina nitron dan maleimida dalam cecair ionik imidazolium pada suhu 25 °C telah dijalankan. Pensiklotambahan antara nitron **1** dan maleimida **2** telah menghasilkan sikloaduk diastereoisomerik dengan nisbah *trans/cis* 1:1 dan 1:2 bagi kedua-dua cecair ionik, [Bmim][PF₆] dan [Bmim][BF₄]. Hasil sikloaduk dalam cecair ionik [Bmim][PF₆] adalah sebanyak 43% berbanding hanya 18% di dalam [Bmim][BF₄]. Apabila tindak balas yang sama dijalankan dalam pelarut kloroform, ianya memberikan sikloaduk diastereoisomerik dalam nisbah 6:0.2 dengan menyebelahi isomer *trans*. Kami beranggapan bahawa interaksi repulsif Van der Waals mendorong keadaan peralihan ekso dengan bantuan cecair ionik imidazolium. Oleh yang demikian, cecair ionik mampu memainkan peranan penting sebagai media kedua di dalam tindak balas dwikutub pensiklotambahan.

Kata kunci: tindak balas perisiklik, 1,3-dwikutub pensiklotambahan, cecair ionik imidazolium

Introduction

Cycloaddition reactions belong to an important group of organic reactions called pericyclic, that are characterized by concerted mechanism proceed *via* cyclic transition states [1]. Woodward-Hoffman rules are used to predict the

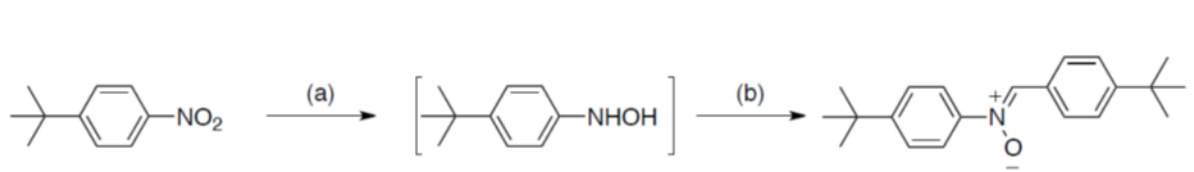
stereochemical features of this pericyclic reaction [2]. In cycloaddition reactions, two or more unsaturated systems react to give a cycle with one less unsaturation. Ionic liquids (ILs) have proved to be alternative solvents and catalysts for the development of the pericyclic reactions [3]. In most cases, an important improvement on the yields and reaction rates has been observed. Hazra et al. observed a good yield in the formation of tetracyclic pyrrolidine/isoxazolidine fused pyrano[3,2-h]quinolines via intramolecular 1,3-dipolar cycloaddition in [Bmim][PF₆] [4].

Thus, the 1,3-dipolar cycloaddition (1,3-DC) reactions has been considered as versatile protocol to generate new C-C bonds, leading to five-membered heterocycles, an essential skeleton in the synthesis of natural products [5]. This reaction furnishes pairs of racemic diastereoisomeric cycloadducts, labelled as *trans* and *cis* with respect to the endo and exo transition states. These two products have markedly different geometries with *trans* diastereoisomer possess an open geometry compared to closed geometry of cisdiastereoisomer. In the case of *cis* isomer, all protons are positioned on the same side with regards to the isoxazolidine ring while in the *trans* isomer, the nitrone-derived hydrogen atom is rendered *trans* to the two hydrogen atoms originally located on the maleimide group.

Not only being regioselective, 1,3-DC also can be highly stereoselective [6]. The mixture of diastereoisomers are obtained depending on the electronic nature of the substituents appended on the two reagents. This outcome originated from the interplay of two generally opposing forces in the transition states, whereby attractive π orbital overlap of unsaturated substituents will favour an endo transition state leading to the formation of isoxazolidine *trans*. On the other hand, repulsive van der Waals steric interactions favour an exo transition state.

Typically, many cycloaddition reactions conducted in ionic liquids (ILs) was Diels-Alder reaction [7]. Nonetheless, the 1,3-dipolar cycloaddition reaction in ILs has not much received attention. The early attempt was reported by Dubreuil and Bazureau in 2000 [8]. Significant rate accelerations and improved yields of cycloadducts were observed for the reaction of imidate and 2-ethoxybenzaldehyde in [Emim][BF₄], [Emim][PF₆] and [Emim][NfO] respectively. Olga and co-workers have studied extensively the Er(OTf)₃ catalyzed 1,3-DC reaction in [Bmim][OTf] which also significantly increase the yield of cycloadducts [9]. Recently, more studies are carried out with the effort to synthesize spiroheterocycles using azomethineylides via catalyzed 1,3-DC reactions [10, 11, 12].

Herein, we described the 1,3-DC reaction between nitrone **1** and maleimide **2** in room temperature ILs. Initially, the nitrone **1** were prepared in two steps synthesis, starting from 4-Tert-Butylnitrobenzene, which first reduced to hydroxylamine derivatives using Rh/C and hydrazine monohydrate. Subsequently, condensation reaction takes place with 4-Tert-Butylbenzaldehyde (Scheme 1). Maleimide **2** was synthesized by simple condensation reaction of maleic anhydride and *p*-toluidine in acetic acid.



Scheme 1. Synthesis of nitrone **1**. Reagents and yields: (a) Rh/C, NH₂NH₂·H₂O, THF, rt, 4 h; (b) 4-Tert-Butylbenzaldehyde, EtOH, rt, 16 h, 44%.

Materials and Methods

Chemical and reagent

Starting materials and reagents used in the reactions were obtained commercially from Sigma Aldrich, Acros Organic and Friendemann Schminidt, were used without purification, unless otherwise indicated. All other reagents and solvents were purified after receiving from commercial suppliers.

Instrument

¹H nuclear magnetic resonance (NMR) spectra were recorded with a JEOL spectrometer (400 MHz) using tetramethylsilane (TMS) as internal standard. ¹³C NMR spectra were recorded on the same instrument at 100 MHz.

The coupling constant (*J*) are given in Hz. IR spectra were obtained with a Perkin Elmer Spectrum GX machine as film or as KBR pellets for all the products. Mass spectroscopy (MS) spectra were recorded with a Bruker instrument. The progression and/or completion of the reactions were monitored by thin-layer chromatography (TLC) using 0.25 mm silica gel plates (Merck Kieselgel 60F₂₅₄ UV indicator), while column chromatography was performed with silica gel (Merck Kieselgel) 600-200 mesh.

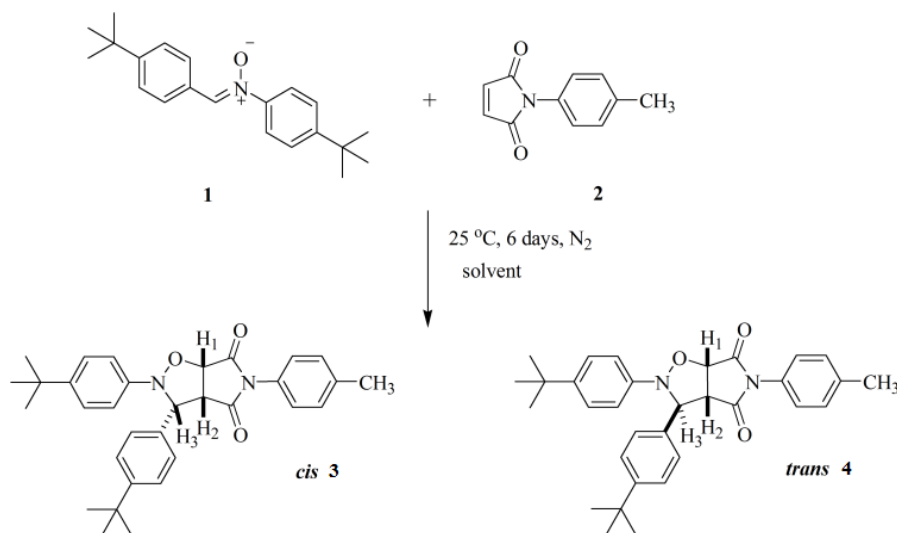
Synthesis of (Z)-4-Tert-Butyl-N-(4-Tert-Butylbenzylidene)aniline oxide **1**

4-Tert-Butylnitrobenzene (0.56 g, 3.12 mmol) was dissolved in THF (15 mL). Rhodium (20 mg, 30 wt.% on carbon, wet) and hydrazine monohydrate (0.19 mL, 3.75 mmol) was added and the progress of the reaction was monitored by TLC. After completion, the solution was filtered through Celite pad and concentrated under reduced pressure to obtain the intermediate hydroxylamine which was directly used in the next step without further purification. The hydroxylamine was dissolved in EtOH (15 mL) and 4-Tert-Butylbenzaldehyde (0.51 mL, 3.12 mmol) was added dropwise to the solution. The reaction mixture was left stirred in the absence of light for 16 hours at ambient temperature. The solvent was concentrated *in vacuo* and the residue was purified by column chromatography (SiO₂, gradient Cyclohexane:EtOAc:Et₃N) to give nitron **1** as yellow solid (44%).

Synthesis of novel diastereomeric isoxazolidine derivatives (**3** & **4**) in ionic liquid

The 1,3-DC reaction between nitron **1** and maleimide **2** was carried by stirring out at room temperature under inert atmosphere in the absence of light for six days. The progress of the reaction was monitored using thin layer chromatography. The cycloadducts were carefully isolated using diethyl ether and cyclohexane and concentrated by evaporation under reduced pressure. The residue was purified by column chromatography (SiO₂, gradient hexane: ethyl acetate) affording both diastereoisomers *cis* and *trans* as colourless solid. [Bmim] with anion BF₄ and PF₆ were used as recyclable solvents for 1,3-dipolar cycloaddition reaction of nitron **1** with maleimide **2** to produce novel isoxazolidine derivatives. The synthesis of the diastereoisomeric adducts were also conducted in chloroform for comparison (Scheme 2).

In a typical procedure, 1 mmol of nitron **1** was mixed with an equivalent of maleimide **2** in [Bmim][BF₄] (2 ml) under stirring at room temperature and the progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was washed with diethyl ethers (3 × 10 ml). The combined organic layers were concentrated *in vacuo* and the resulting product was directly charged on silica gel column and eluted with a mixture of ethyl acetate:hexane to afford pure isoxazolidines.



Scheme 2. Synthesis of diastereoisomeric cycloadducts **3** and **4** via cycloaddition between nitron **1** and maleimide **2** at 25 °C

Results and Discussion

[Bmim][PF₆] was found to give better yield of 43% as to compare with only 18% in [Bmim][BF₄] (Table 1). This results is in agreement from previous observation from other studies involving cycloaddition reactions in imidazolium based ILs. Chakraborty and Luitel have demonstrated the application of imidazolium ILs as solvents in their cycloaddition reaction of *N*-Benzyl fluoronitron with maleimide derivatives. In all cases, they found the ratio of the diastereoisomer is 3:1, favouring *cis* cycloadduct [13]. Ganesh et al. also observed similarly the exclusive formation of *cis* fused products in highly stereoselectivity intramolecular 1,3-dipolar cycloaddition of azomethineylides as well as nitrones[14].

Table 1. 1,3-Dipolar cycloaddition reactions of nitron 1 with maleimide 2

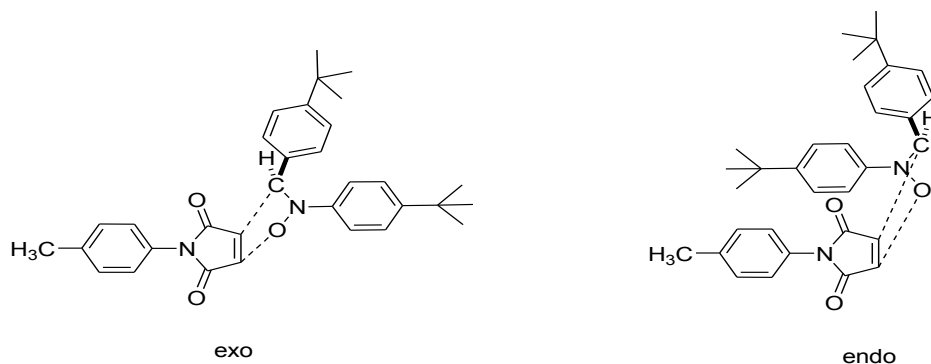
Entry	Solvent ^a	<i>cis</i> (3)/ <i>trans</i> ratio(4) ^b	Yield (%)
1	[Bmim][BF ₄]	2:1	18
2	[Bmim][PF ₆]	1.1:1	43
3	CHCl ₃	0.2:6	36

^aReaction conditions: nitron 1 (1 mmol), maleimide 2 (1 equivalent), 2 mL of respective ILs or 4 mL of CHCl₃, N₂ atmosphere, rt,

^bCycloadducts were characterized by IR, ¹H NMR, ¹³C NMR and MS spectral data

In the case of *cis* cycloadduct, the prominent signal for proton H₃ and H₁ are both doublet, while triplet for H₂. By contrast, *trans* cycloadducts, signal for proton H₃ is singlet while doublet for H₁ and H₂. It is shown that [Bmim][BF₄] and [Bmim][PF₆] gave cycloadducts in 1:2 and 1:1.1 ratio, respectively, favouring *cis* diastereoisomer. This results is staggering given that a typical uncatalyzed 1, 3-DC of nitron and maleimide in chloroform leads to the solely formation of *trans* cycloadduct with the ratio of 6:0.2. In addition, mass spectral analysis of the cycloadducts provided evidence for the success of the cycloaddition reactions. The mass spectrum shows the present of molecular ion peak at the base peak *m/z* = 519.26, 497.27 and 332.20, respectively.

For the formation of major cycloadduct, these results can be rationalized by an *exo* approach of nitron which has *Z* configuration while an *endo* approach leads to the formation of minor cycloadduct (Scheme 3).



Scheme 3. *Exo/endo* approach of nitron to maleimide in cycloaddition reaction

ILs have shown powerful catalytic properties to accelerate the Diels Alder reaction due to its ionic features. We do believe that ILs contribute to the accessibility of *exo* transition state, which in return give more *cis* diastereoisomer.

In the meantime, we are trying to investigate further this kind of reactions with elongated 1,3-dipole compounds and dipolarophiles.

Characterization

Representative data for synthesis of (Z)-4-Tert-Butyl-N-(4-Tert-Butylbenzylidene)aniline oxide 1: M.p. = 152.5 – 154.4 °C; ¹H NMR (300.1 MHz, CDCl₃): δ_H 8.35 – 8.30 (2H, m, ArH), 7.88 (1H, s, CH), 7.72 – 7.67 (2H, m, ArH), 7.52 – 7.46 (4H, m, ArH), 1.35 (18H, s, CH₃); ¹³C NMR (75.5 MHz, CDCl₃): δ_C 154.4 (ArC), 153.3 (ArC), 146.8 (ArC), 134.2 (CH), 129.1 (ArCH), 128.3 (ArC), 126.1 (ArCH), 125.7 (ArCH), 121.4 (ArCH), 35.2 (qC), 35 (qC), 31.4 (CH₃), 31.3 (CH₃); MS (ES⁺) m/z 332.0 ([M+Na]⁺, 95), 641.0 (100); HRMS (ES⁺) m/z calculated for C₂₁H₂₇NONa 332.1990 [M+Na]⁺, found 332.1994.

Representative data for cis cycloadduct 3: Mp: 196.6-196.8 °C; ¹H NMR (400 MHz; CDCl₃) δ_H 7.41 (2H, d, J= 8.40 Hz, ArCH), 7.37 (2H, d, J= 8.40 Hz, ArCH), 7.27 (2H, d, J= 9.16 Hz, ArCH), 7.13 (2H, d, J= 8.08 Hz, ArCH), 7.05 (2H, d, J= 8.80 Hz, ArCH), 6.68 (2H, d, J= 8.44 Hz, ArCH), 5.30 (1H, d, J= 8.04 Hz, CH), 5.06 (1H, d, J= 8.80 Hz, CH), 4.03 (1H, t, J= 8.44 Hz, CH), 2.31 (3H, s, CH₃), 1.30 (9H, s, CH₃), 1.26 (9H, s, CH₃); ¹³C NMR (100 MHz; CDCl₃) δ_C 173.2 (C=O), 156.3, 151.8, 149.2, 146.3, 145, 141.4, 138.5, 137.2, 132, 131.3, 129.7, 127.4, 117.3 (CH), 71.2 (CH), 54.6 (CH), 34.8 (quat. C), 34.5 (quat. C), 31.5 (CH₃), 31.2 (CH₃), 21.2 (CH₃); IR ν_{max} (KBr) cm⁻¹: 2956.05 cm⁻¹ (sp³ CH), 1608.84 cm⁻¹ and 1461.15 cm⁻¹ (aromatic C=C), 1722.79 cm⁻¹ (C=O), 1197.36 cm⁻¹ (C-N), MS (ESI⁺) m/z 519.26 ([M+ Na]⁺, 100%).

Representative data for trans cycloadduct 4: Mp: 196.5-196.7°C; ¹H NMR (400 MHz, CDCl₃) δ_H 7.52 (2H, d, J= 8.44 Hz, ArCH), 7.44 (2H, d, J= 8.44 Hz, ArCH), 7.26 (2H, d, J= 8.80 Hz, ArCH), 7.09 (2H, d, J= 9.16 Hz, ArCH), 7.06 (2H, d, J= 9.88 Hz, ArCH), 6.34 (2H, d, J= 8.44 Hz, ArCH), 5.78 (1H, s, CH), 5.07 (1H, d, J= 7.32 Hz, CH), 4.01 (1H, t, J= 7.32 Hz, CH), 2.29 (3H, s, CH₃), 1.34 (9H, s, CH₃), 1.28 (9H, s, CH₃); ¹³C NMR (100 MHz; CDCl₃) δ_C 173 (C=O), 1561.1, 146.7, 145.8, 143.7, 139.3, 139.1, 136, 135.9, 129.8, 129.6, 128.4, 128.3, 113.9 (CH), 69.6 (CH), 57.3 (CH), 34.5 (quat. C), 34.3 (quat. C), 31.5 (CH₃), 31.3 (CH₃), 21.2 (CH₃); IR ν_{max} (KBr) cm⁻¹: 2956.05 cm⁻¹, 1608.84 cm⁻¹ and 1461.15 cm⁻¹ (aromatic C=C), 1722.79 cm⁻¹ (C=O), 1197.36 cm⁻¹ (C-N); MS (ESI⁺) m/z 497.27 ([M+ H]⁺, 100%).

Conclusion

Considering the environmental pollution by using conventional organic solvents, ILs have become an alternative reaction media for the development of green synthetic strategies in 1,3-DC. Two ionic liquids, [Bmim][BF₄] and [Bmim][PF₆] has facilitated the course of 1,3 DC of nitron and maleimide with improved results on the yield of the cycloadducts. In the future, we would like to explore the use of microwaves as conventional heating sources. ILs will be heated very quickly, thus, providing shorter reaction times and efficient reaction due to microwave irradiation.

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