Endo Selective Diels–Alder Reactions of Furan in Ionic Liquids

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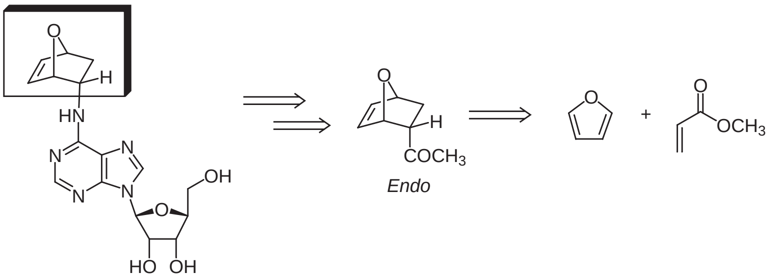
Abstract: Diels–Alder reactions of the heteroaromatic diene furan proceed with enhanced isolated yields and reversal of *endo*/*exo* selectivity (2:1 *endo* vs *exo*) in the ionic liquids [bmim]BF_4 and [bmim]PF_6 compared to conventional methods. The potential utility of ionic liquids as solvents in Diels–Alder reactions of thiophene and pyrrole derivatives has also been demonstrated.

Key words: Diels–Alder reactions, heterocycles, solvent effects, furans, pyrroles

In the course of our investigations towards the total synthesis of adenosine receptor agonists containing an *endo* 5-substituted 7-oxabicyco[2.2.1]hept-2-ene moiety we encountered unfavourable *endo*/*exo* selectivity using conventional Diels–Alder methodologies in the preparation of 7-oxabicyco[2.2.1]hept-2-ene precursors (Scheme 1).[1] Under most conventional conditions the *exo* isomer of 5-substituted 7-oxabicyco[2.2.1]hept-2-ene systems is the major isomer.[2] The use of furan as a diene in Diels–Alder reactions is also plagued by several other difficulties. Furan is Lewis acid sensitive and, when reacted with dienophiles, the resulting products readily undergo retro-Diels–Alder reactions to reform starting materials or are cleaved to form 2-substituted furans. Literature examples of Diels–Alder reactions of furan include those with very long reaction times,[3] ZnI_2 at 40 °C in a sealed tube,[2] high pressure (20 000 atm),[4] and the use of zeolites.[5] Attempts to improve yields of these reactions by using excess diene lead to by-product formation and hence purification of sensitive cycloadducts is further complicated.

Ionic liquids have been gaining much popularity as solvents in a number of synthetic methodologies[6] including applications in Diels–Alder chemistry.[7] However, the range of dienes utilized in ionic liquid solvents remains limited and typically involves such dienes as cyclopentadiene. Some of the highest *endo*/*exo* ratios have been obtained for the reaction of methylacrylate and cyclopentadiene in chloroaluminate based ionic liquids.[7c] Use of these Lewis acidic ionic liquids precludes the use of furan and other heteroaromatic dienes due to their lack of stability in the presence of common Lewis acids. The propensity of Diels–Alder adducts derived from furan to undergo retro-Diels–Alder reactions, especially upon heating, prohibit the use of ionic liquids that melt at or above room temperature as solvents for these reactions. Hence, room temperature ionic liquids such as 1-butyl-3-methylimidazolium tetrafluoroborate, [bmim]BF_4, (mp –81 °C)[8] and 1-butyl-3-methylimidazolium hexafluorophosphate, [bmim]PF_6 (mp 4 °C)[8] were considered viable candidates for solvents to be used in Diels–Alder reactions involving furan and other heteroaromatic dienes.

We report herein the use of the air and moisture stable ionic liquids [bmim]BF_4 and [bmim]PF_6 as solvents for Diels–Alder reactions of furan with dienophiles of specific interest towards the total synthesis of potential adenosine agonists. We have shown that these solvents also have potential for use in Diels–Alder reactions of thiophene and *t*-BOC-pyrrole dienes. These reactions have been shown to proceed with increased isolated yields of adducts, and in the case of furan reacting with methyl acrylate, with *endo* selectivity. This *endo* selectivity is the opposite to that obtained using conventional methods. The extension of ionic liquid methodology to heteroaromatic dienes in Diels–Alder reactions demonstrates how these solvents increasing-



Scheme 1 Retrosynthetic analysis of potential adenosine receptor agonist

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ly provide practical alternatives to conventional solvents for synthetic applications.

Typically 1.4 equivalents of the diene was reacted with the dienophile in the presence of 30 mol% or 100 mol% of a ZnI_2 in [bmim]BF_4 or [bmim]PF_6. [Bmim]PF_6 had been exhaustively washed with de-ionized water until pH neutral and both [bmim]BF_4 and [bmim]PF_6 were dried on high-vac prior to use. With the exception of entries 13 and 15 in Table 1 none of the reactions proceeded without the inclusion of this mild Lewis acid. Indeed it had been shown in previous studies that ZnI_2 catalyzed the reaction of furan with methyl acrylate.[2] Attempts to use stronger Lewis acids such as $BF_3{\cdot}OEt_2$ or chloroaluminate based ionic liquids such as [bmim]Al_2Cl_7 resulted in the decomposition of the reactants. All reactions in Table 1 were conducted at room temperature to avoid retro-Diels–Alder reactions of the adducts once they had formed. Reaction times were typically 48–72 hours; these were similar to those reported elsewhere in the literature for reactions that gave poorer results under conventional conditions. Reactions were stopped after no further change in product mixtures were observed by gas chromatography with the balance of starting material remaining unreacted.

In our study it was demonstrated that use of 30 mol% of ZnI_2 afforded a slightly better *endo*/*exo* ratio than the use of a full equivalent of ZnI_2 (Table 1, entry 1 vs 2 and 3 vs 4). Use of a full equivalent of ZnI_2 seems to have promoted formation of more *exo* adduct (e.g. both *endo* and *exo* formation are catalyzed in the presence of 1 full equivalent of ZnI_2) resulting in an increased isolated yield of adducts with a slightly decreased selectivity (i.e. entry 1 vs entry 2). In all cases, the use of ZnI_2 to catalyze the reaction in [bmim]BF_4 or [bmim]PF_6 resulted in a reversal of the *endo*/*exo* ratio as compared to those reactions conducted under other conditions without ionic liquids.[2] Similar *endo* selectivity in ionic liquid solvents has been attributed to the highly ordered hydrogen-bonded nature of ionic liquids that leads to stabilisation of the more polar *endo* activated complex and/or association of reagents in a ‘solvent cavity’ during the rate determining step.[7b] The use of a full equivalent of ZnI_2 in these reactions served to increase the overall chemical yield of the Diels–Alder adduct isolated from the ionic liquid reaction solutions. It is noteworthy that Table 1 shows isolated yields that are much improved over those reported elsewhere and that when methyl acrylate is the dienophile the *endo*/*exo* ratio favour the formation of the *endo* adducts rather than the *exo*.[2,4,5,9] For example, Table 1, entry 1 shows that in [bmim]BF_4 a 67% isolated yield is obtained with a 2.3:1 *endo*:*exo* ratio compared to a 55% yield with a 1:2 *endo*:*exo* ratio under solventless conditions.[2] In agreement with literature reports we obtained exclusively *exo* adducts when furan was reacted with maleic anhydride.[10]

Use of freshly prepared, pH neutral, and dried [bmim]PF_6 generally resulted in a decrease in the isolated yields of adducts as compared to those reactions conducted in dry [bmim]BF_4. However, they were still higher yields than those obtained under conventional means. This may be due to increased solubility of adducts in [bmim]PF_6 resulting in difficulty in extraction of these products from the reaction mixtures using common organic solvents (see typical procedure). Since [bmim]BF_4 is readily soluble in water whereas the Diels–Alder adducts extract into the organic phase during extraction [bmim]BF_4 could be easily separated from the desired product. However, the hydrophobic nature of [bmim]PF_6 complicated the separation of the adducts from the ionic liquid solvent using a simple organic–aqueous phase extraction.

We sought to extend the use of ionic liquids as solvents in the Diels–Alder reactions of other heteroaromatic dienes that pose some of the same difficulties as furan. Hence, we reacted thiophene with dimethylacetylene dicarboxylate, DMAD, in the presence of 30 mol% of ZnI_2 in [bmim]BF_4 at room temperature. This reaction afforded a 44% isolated yield of the Diels–Alder adduct upon purification by column chromatography. This is an improvement over conventional methodology in which typically lower yields are obtained for this reaction.[11] We also reacted *t*-BOC-pyrrole with DMAD under similar conditions but in the absence of ZnI_2. Although the isolated yield of the adduct was low (i.e. 23%) this is still comparable to those reported elsewhere for related pyrrole Diels–Alder adducts formed in an uncatalyzed reaction.[12] The crystal structure of this adduct is shown in Figure 1. This structure confirms the assigned structure for this adduct as the ‘mono’ Diels–Alder adduct. It is significant that the adducts obtained for Table 1, entries 14 and 15 did not undergo further Diels–Alder reaction with diene present in the system as they formed.[13]

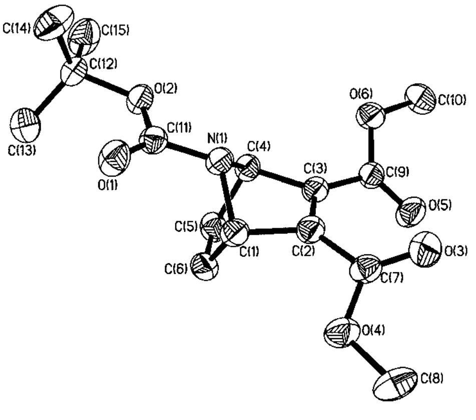
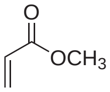
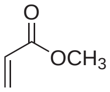
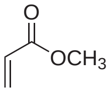
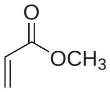
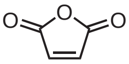
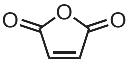
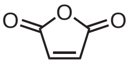
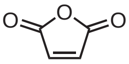
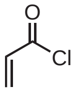
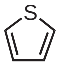
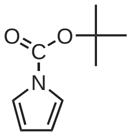


Figure 1 X-Ray crystal structure of 7-(*tert*-butyl) 2,3-dimethyl-7-azabicyclo[2.2.1]hepta-2,5-diene-2,3,7-tricarboxylate; adduct from Table 1, entry 15

The use of the ionic liquids [bmim]BF_4 and [bmim]PF_6 in the Diels–Alder reactions of furan, thiophene, and *t*-BOC-pyrrole with simple dienophiles such as methylacrylate, maleic anhydride, and DMAD affords higher isolated yields of adducts than those methods previously reported. Interestingly, these ionic liquid systems induce a reversal of the *endo*/*exo* selectivity in the reaction of furan with methylacrylate. [Bmim]BF_4 is a superior solvent to [bmim]PF_6 since it allows products to be more easily iso-

Table 1 Diels–Alder Reactions of Heteroaromatic Dienes in [bmim]BF_4 and [bmim]PF_6

Entry	Ionic Liquid	Diene	Dienophile	ZnI_2 (mol%)	Yield (*endo*/*exo*)[a,b]	Literature yield (*endo*/*exo*)
1	[bmim]BF_4			30	67% (2.3:1)	55% (1:2)[2]
2	[bmim]BF_4			100	75% (1.8:1)	–
3	[bmim]PF_6			30	42% (2.3:1)	–
4	[bmim]PF_6			100	73% (1.4:1)	–
5	[bmim]BF_4			30	79% (0:1)	[c]
6	[bmim]BF_4			100	73% (0:1)	–
7	[bmim]PF_6			30	38% (0:1)	–
8	[bmim]PF_6			100	52% (0:1)	–
9	[bmim]BF_4		$H_3CO_2C{-}{\equiv}{-}CO_2CH_3$	30	32%	20%[13]
10	[bmim]BF_4		$H_3CO_2C{-}{\equiv}{-}CO_2CH_3$	100	22%	–
11	[bmim]PF_6		$H_3CO_2C{-}{\equiv}{-}CO_2CH_3$	30	19%	–
12	[bmim]PF_6		$H_3CO_2C{-}{\equiv}{-}CO_2CH_3$	100	4%	–
13	[bmim]BF_4			0	21%	[c]
14	[bmim]BF_4		$H_3CO_2C{-}{\equiv}{-}CO_2CH_3$	30	44%	[d]
15	[bmim]BF_4		$H_3CO_2C{-}{\equiv}{-}CO_2CH_3$	0	23%	40%[e]

[a] All yields are isolated yields.

[b] Structures of adducts confirmed by ^1H NMR, ^{13}C NMR, and MS; *endo*/*exo* ratios determined by ^1H NMR.

[c] Product has been synthesized but no yields reported (ref.[10] for entry 5, ref.[1] and ref.[9] for entry 13).

[d] Desulfurized product of thiophene and dicyanoacetylene has been reported in 8% yield.[11]

[e] 40% yield of trimethyl pyrrole-*N*,3,4-tricarboxylate (product of methyl pyrrole-*N*-carboxylate and DMAD which has undergone retro-Diels–Alder to lose acetylene).[14]

lated in higher yields. Both ionic liquids allow the use of lower reaction temperatures for these Diels–Alder reactions. The use of the *endo* enriched 7-oxabicyclo[2.2.1]hept-2-enes obtained from these reactions as precursors to potential adenosine agonists is under investigation.

Typical Procedure

[bmim]BF$_4$ (2.0 mL) was heated under vacuum at 60 °C for 2 h in a 25 mL round bottom flask. ZnI$_2$ (0.96 g, 3.0 mmol, weighed in glove box into oven-dried vial) was added under a stream of N$_2$ and the mixture was heated under vacuum for a further 2 h. Methyl acrylate (0.90 mL, 10.0 mmol) was injected after cooling and sealing the flask with a septum. This stirred for 15 min in a r.t. water bath, after which time freshly distilled furan (1.02 mL, 14.0 mmol) was injected. This was stirred for 48 h at r.t., after which time the reaction was diluted with 100 mL EtOAc. This was washed with 0.1 M Na$_2$S$_2$O$_3$ (1×50 mL) and water (1×50 mL), then dried (MgSO$_4$), filtered, and concentrated to a yellow oil. The crude product was purified via flash chromatography using 10:1 hexanes:EtOAc, followed by a 2:1 mixture. The product was isolated as a yellow oil (0.665 g, 4.31 mmol, 67%). ^{1}H NMR indicated an *endo*:*exo* ratio of 2:1. ^{1}H NMR: δ = 1.59 (dd, H3$_n$ *endo*, *exo*), 2.06–2.19 (m, 1 H, H3 × *endo*, *exo*), 2.44 (q, H2 *exo*), 3.12 (quintet, H2 *endo*), 3.65 (s, CH$_3$ *endo*), 3.76 (s, CH$_3$ *exo*), 5.01–5.19 (m, 2 H, H1 *endo*, *exo*, H4 *endo*, *exo*), 6.34 (ddd, H5 *endo*, H6 *endo*), 6.39 (ddd, H5 *exo*, H6 *exo*); ^{13}C NMR: δ = 28.4, 28.9, 42.5, 51.6, 52.0, 77.8, 78.6, 78.9, 80.7, 132.4, 134.5, 136.9, 172.5, 174.1; MS (ES+): 154.1.

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