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Diels-Alder Reactions in Chloroaluminate Ionic Liquids: Acceleration and Selectivity Enhancement

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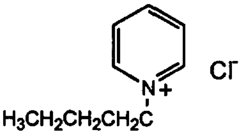
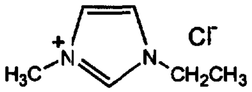
Abstract: The utility of room temperature chloroaluminate ionic liquids as solvent and catalyst for the synthetically important Diels-Alder reaction was studied. The $AlCl_3$-1-ethyl-3-methyl-1*H*-imidazolium chloride medium proved to be ideally suited for Diels-Alder reactions. Endo selectivity and rate enhancement were observed for the cyclopentadiene/methyl acrylate Diels-Alder reaction.

INTRODUCTION

The use of ambient temperature chloroaluminate ionic liquids, $AlCl_3$:MCl, where MCl is either *N*-1-butylpyridinium chloride (BPC), or 1-ethyl-3-methyl-1*H*-imidazolium chloride (EMIC), as solvent/catalyst for the synthetically important Diels-Alder reaction, have never been reported.



BPC



EMIC

This is unfortunate, because chloroaluminate ionic liquids have inherent properties that make them ideal for carrying out Diels-Alder reactions. Room temperature chloroaluminate ionic liquids are polar, exhibit high solubility towards organic and inorganic solutes, and most importantly exhibit variable Lewis acidity. Selectivity and reactivity of Diels-Alder reactions are strongly influenced by the Lewis acidity of the medium. Unlike most reaction media, the composition of chloroaluminate ionic liquids can be easily varied from basic (EMIC or BPC in excess) to acidic ($AlCl_3$ in excess) (1). The variable Lewis acidity of chloroaluminate ionic liquids is unique and should have profound effects on the rates and selectivities of Diels-Alder reactions. Furthermore, protons in ambient temperature chloroaluminate ionic liquids function like Brϕnsted superacids with Hammett acidity functions, H_0, ranging from -12.6 (1.04 : 1.0 mol ratio $AlCl_3$-EMIC) to -18 (2 : 1 mol ratio $AlCl_3$-EMIC) (2, 3). This "doubly acidic" medium should significantly influence Diels-Alder reactions which are known to be influenced by Lewis and Brϕnsted acid catalyst. These acid catalysts greatly accelerate reaction rates, and enhance diastereo- and regioselectivity (4, 5).

In recent years, as a result of the importance of Diels-Alder reactions in the synthesis of natural products and physiologically active molecules, increased interest has been placed on the development of special physical and catalytic methods for the purpose of improving the rate and/or selectivity of $[4\pi + 2\pi]$-cycloaddition reactions (5). Here we wish to report the first study on the utility of room temperature chloroaluminate ionic liquids as solvent/catalyst for the synthetically important Diels-Alder reaction.

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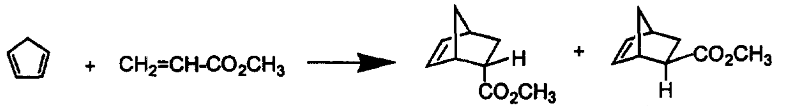
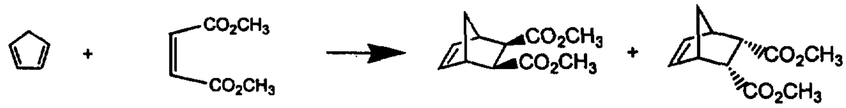
RESULTS AND DISCUSSIONS

The utility of room temperature chloroaluminate ionic liquids as solvent/catalyst for Diels-Alder reactions was investigated using two classic Diels-Alder reactions: that between cyclopentadiene (1) with methyl acrylate (2) to give endo/exo products (3) and (4);



(1) (2) (3) (4) (1)



(2)

(1) (5) (6) (7)

and that between (1) and dimethyl maleate (5) to give products (6) and (7). The above reactions have been widely investigated in a variety of solvents and are considered model Diels-Alder reactions.

Equimolar **1** and **2** were allowed to react under nitrogen in the basic (48% $AlCl_3$) melt for 22 and 72 hours (6). GC-MS analysis of the crude reaction products revealed, as expected, both the endo (3) and exo (4) products. As shown in Table 1, the product yield increased as a function of time, while the stereochemical selectively remained essentially constant (endo/exo ratio ~ 5/1). The same general trend was observed when equimolar amounts of (1) and (2) was allowed to react in the acidic (51% $AlCl_3$) melt. The product yield increased with time and the stereochemical selectivity remained essentially the same at all reaction times. Of significant interest, however, is the dramatic enhancement in selectivity in going from the basic to the acidic melt. A four fold increase in selectivity was observed (endo/exo ratio = 19/1 in the acidic melt). The observed endo selectivity enhancement in the 51% melt is a direct result of the increase in Lewis/Brϕnsted acidity of the medium, while the observed 5:1 endo/exo product ratio in the basic melt is a reflection of the polarity of the medium. No molecular $AlCl_3$ exist in the medium.

Table 1: Diels-Alder Reactions of **1** and **2** in Room Temperature Chloroaluminate Ionic Liquids[a].

Melt Composition (% $AlCl_3$)	Reaction Time (Hrs.)	Endo/Exo Ratio	% Yield	$10^4 k_2$ ($M^{-1} sec^{-1}$)
48	22	4.88	32.3	
48	72	5.25	95	12.5
51	22	19	53	
51	72	19	79.4	297

a) Average values of at least duplicate runs. Average deviation = ± 0.05 for endo/exo ratios, and ± 10% for kinetic studies.

Literature data on the effect of solvent on the rate and selectivity of the cyclopentadiene/methyl acrylate Diels-Alder reaction are shown in Table 2 (7). As shown in Table 2, the rate and selectivity of the reaction increases as the polarity of the medium increases,

Table 2: Solvent Effects on the Rate and Selectivity of the cyclopentadiene/methylacrylate Diels-Alder Reaction.[a]

solvent	T, °C	[1], (M)	[2], (M)	ratio of 3:4	10^4 k_2 ($M^{-1}sec^{-1}$)
EAN	25 ± 2	0.20	0.20	6.7	
EAN	20.0 ± 0.2	0.10	0.20	6.7	1.7
water	21 ± 1	0.00040	0.012		30
water	25	0.15 (0.30)	0.15 (0.30)	9.3 (5.9)	
water	20	0.15	0.15	7.4	
1-chlorobut.[b]	35				0.53
benzene	35	1.25	1.25	2.8	
ethanol	30			5.2	
methanol	26			7.0	
formamide	20	0.15 (0.30)	0.15 (0.30)	6.7 (6.7)	

a) Data from reference 7. b) 1-chlorobutane.

with water, a polar protic solvent showing the most significant influence. The dramatic rate and selectivity enhancement observed for Diels-Alder reactions in water is attributed to two factors: (1) hydrophobic association of reactants; and (2) hydrogen bonding to the activating group of the dienophile (7-11). Ethyl ammonium nitrate (EAN), a low melting solid similar to $AlCl_3$-EMIC and related chloroaluminate melts, also exhibited some influence on the rate and selectivity of the reaction. The acidic $AlCl_3$-EMIC melt is far superior to both water and EAN as a solvent for the cyclopentadiene/methyl acrylate Diels-Alder reaction. However, unlike EAN, chloroaluminate ionic liquids are not potential explosives. Furthermore, unlike water, most organic molecules are very soluble in room temperature ionic liquids. This means that reactions can be performed at synthetically useful scales in chloroaluminate ionic liquids.

The kinetics of the reaction between 1 and 2 were studied in the basic and acidic melts at 25 °C under psuedo-first order conditions. In the basic and acidic melts, 3.25 M (1) and 1.62 M (2) were allowed to react and the appearance of (3) and (4) was followed by GC analysis (internal standard = decane). The second order rate constant, k_2, for the basic and acidic melts was 12.5 x 10^{-4} M^{-} s^{-} and 297 x 10^{-4} M^{-} s^{-}, respectively. The k_2 value in the acidic melt is 24 times greater than that observed in the basic melt.

Compared to water and EAN, the rate of reaction in the acidic melt is 10 times faster than in water and 175 times faster than that observed in EAN. The rate of reaction in the basic melt while 2 times slower than in water, is 7 times faster than in EAN. It is quite evident that molten salts, in particular, acidic room temperature molten salts are far superior solvents for the synthetically important Diels-Alder reaction. Endo selectivity is significantly enhanced, product yields are favorable, and reaction rates are far superior than that observed in traditional polar or nonpolar solvents.

The reaction of **1** and **5** in the basic and acidic melts was also investigated. Results were quite similar to that observed for **1** and **2**. The acidic melt again proved to generate far superior results when compared to the basic melt, and other solvents such as water, ethanol and microemulsions. We are currently conducting kinetic studies on the above reaction.

In conclusion, we have presented evidence for the utility of room temperature chloroaluminate ionic liquids as solvent/catalyst for the synthetically important Diels Alder reaction. Reaction rates and endo/exo selectivity proved to be far superior to that observed in traditional polar and nonpolar Diels-Ader reaction media. In addition, product yields were sufficiently high, and the high solubility of organic solutes in the melts allows for reactions to be performed at synthetically useful scales.

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6 0.00252 moles (**1**) was allowed to react with 0.00252 moles (**2**) in a 25 mL flask containing 6 mL of the melt. The reaction mixture was quenched with 2 mL of chilled water, neutralized with 2-3 mL of NaOH, and the organics extracted with CH_2Cl_2.

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