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Catalysis by Lithium Perchlorate in Dichloromethane: Diels-Alder Reactions and 1,3-Claisen Rearrangements

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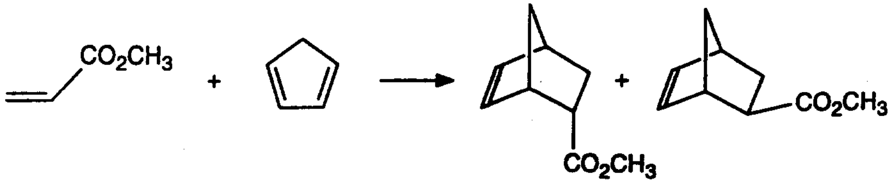
Abstract: Lithium perchlorate suspended in dichloromethane is an efficient catalyst (4 - 25 mol-%) for stereoselective Diels-Alder, hetero-Diels-Alder and regioselective 1,3-Claisen rearrangements; this process is milder, safer and environmentally less precarious than the use of 1 - 5 molar solutions of $LiClO_4$ in ether described previously in the literature.

Concentrated solutions of lithium perchlorate in diethyl ether (1 - 5 M) are known to induce a wide variety of transformations, including Diels-Alder reactions, Mukaiyama aldol and Michael additions and 1,3-Claisen rearrangements[1]. A clear disadvantage of such a reaction medium concerns the environmental problem associated with the disposal of the excess perchlorate and with the possibility of explosions in rare cases[2]. Recently we discovered that a catalytic amount of $LiClO_4$ (3 mol-%) suspended in dichloromethane is much more effective in mediating Mukaiyama aldol and Michael additions than a 3 mol-% solution of $LiClO_4$ in ether[3]. The salt acts as a mild Lewis acid.

The dramatically enhanced activity of catalytic amounts of $LiClO_4/CH_2Cl_2$ relative to $LiClO_4$/ether led us to study other reaction types known to be mediated by the traditional protocol based on 1 - 5 M ether solutions of $LiClO_4$[1]. Here we report on stereoselective Diels-Alder and Hetero-Diels-Alder reactions as well as regioselective 1,3-Claisen rearrangements using catalytic amounts of $LiClO_4$ in dichloromethane.

Diels-Alder and Hetero-Diels-Alder Reactions

The reaction of methyl acrylate **1** with cyclopentadiene **2** is accelerated by the presence of 4 mol-% $LiClO_4$, the endo/exo ratio **3**/**4** also being influenced by this Lewis acid (Table 1). The highest endo/exo ratio turned out to be 7.3 using 25 mol-% $LiClO_4$ at -15°C. This compares favorably with the result obtained by performing the reaction in 5 M $LiClO_4$/ether (3/4 = 8.0)[1]. Nevertheless, the degree of acceleration is modest. In the absence of $LiClO_4$ conversion is 38% at -15° after a reaction time of 24 h, the endo-exo ratio being 4 : 1.

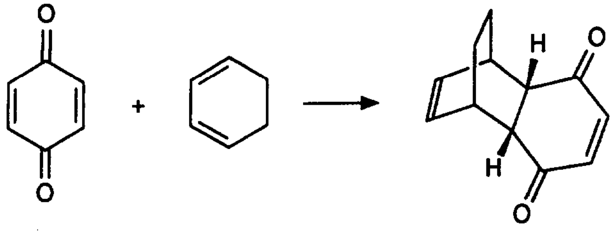


1 **2** **3** **4**

Table 1. Diels-Alder Reaction of **1** and **2** in CH_2Cl_2

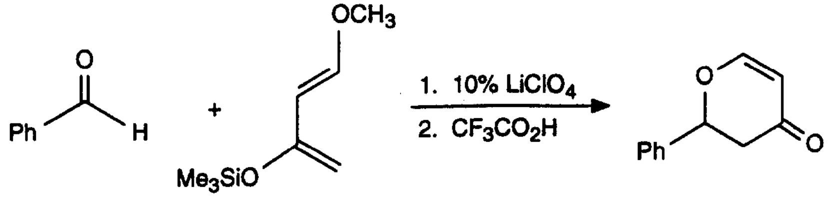
Entry	$LiClO_4$ (mol-%)	Time (h)	Temp. (°C)	Conversion (%)	endo/exo ratio
1	0	16	22	94	3.8
2	0	24	-15	38	4.0
3	4	16	22	97	4.9
4	30	18	22	100	6.0
5	25	24	-15	75	7.3

Upon reacting p-quinone **5** with cyclohexadiene **6** in the presence of 7 mol-% $LiClO_4$ in CH_2Cl_2, conversion to the single (endo) product **7** was complete (98%) at room temperature within 3 hours. In the absence of catalyst, conversion is only 90% in a reaction which was run overnight. Again, the degree of rate acceleration is fairly modest.



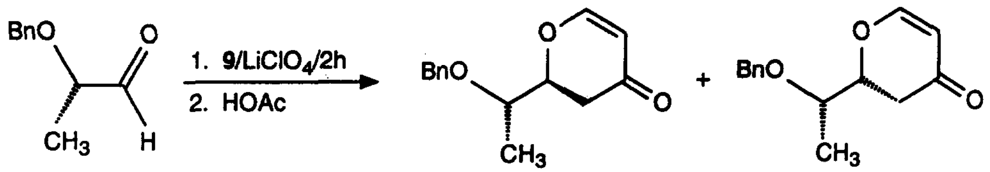
5 **6** **7**

In the case of Hetero-Diels-Alder reactions, rate acceleration by $LiClO_4$ is much more pronounced. For example, benzaldehyde **8** reacts with the Danishefsky diene **9** within 23 hours to form 72% of the adduct **10** at room temperature (following acidic workup[4]), whereas in the absence of catalyst no reaction occurs at all.



8 **9** **10**

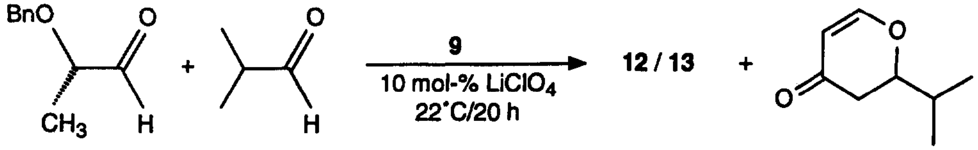
In the case of the chiral aldehyde **11**, the rate of the cycloaddition reaction is considerable higher, and high levels of chelation control[5] result. The ratio of chelation to non-chelation controlled products **12**/**13** depends slightly on the amount of catalyst employed. Essentially complete chelation control is possible using 15 mol-% of $LiClO_4$. Thus, diastereoselective catalysis is involved. Similar stereoselectivity has been observed by Danishefsky upon using stoichiometric amounts of $MgBr_2$[6].



11 **12** **13**

6 mol-% $LiClO_4$	90	:	10
15 mol-% $LiClO_4$	>95	:	<5

The above observations in the area of chelation control are not only of synthetic, but also of mechanistic interest. Eliel has pointed out that if Cram chelates are in fact true intermediates in the reaction of Grignard reagents with α-alkoxy ketones, enhanced rates should result[7]. He demonstrated that this is indeed the case, higher rates correlating with higher degrees of stereoselectivity in favour of chelation controlled products. Breslow has "drawn a provocative analogy between this simultaneous effect of chelation on reactivity and its stereoselectivity and the relationship between an enzyme and its substrate where these two features also often go hand in hand"[8]. In our own work we have recently shown that $LiClO_4$ (3 mol-%) catalyzes the Mukaiyama aldol addition of ketene ketals to aldehydes, and that α-alkoxy aldehydes such as **11** react considerably faster than normal aldehydes[3]. The same phenomenon is observed in the present Hetero-Diels-Alder reactions. In order to get a better picture of the rate enhancement due to chelation effects in these cycloaddition reactions, a 1 : 1 : 1 competition experiment involving the diene **9**, the alkoxy aldehyde **11** and 2-methylpropanal **14** in CH_2Cl_2 was carried out at room temperature. None of the adduct **15** derived from 2-methylpropanal was observed.

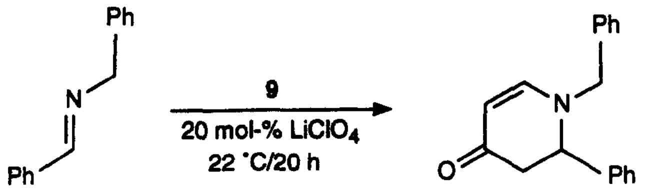


11 **14** **15**

>99 : <1

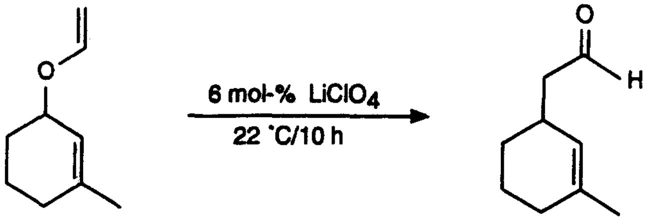
Obviously, the Breslow analogy[8] is of particular relevance in these cycloaddition reactions and in the previously described aldol additions[3], because in these systems enhanced rates due to chelation phenomena originate from a catalytic process. Related is the interesting observation of Nakai that in $Eu(fod)_3$ catalyzed enolsilane additions the benzyl-protected aldehyde **11** reacts somewhat faster than the $tBu(Me)_2Si$-protected analog[9].

Hetero-Diels-Alder reactions with aldimines are known to be less efficient than the analogous reactions with aldehydes, because the C-N double bond is less reactive than the normal aldehyde function[10]. Nevertheless, we reacted the aldimine **16** with the Danishefsky diene **9** in the presence of 20 mol-% of $LiClO_4$ in CH_2Cl_2 at room temperature[11]. After 20 h an isolated yield of 54% of the cycloaddition product **17** was obtained following desilylative aqueous workup.

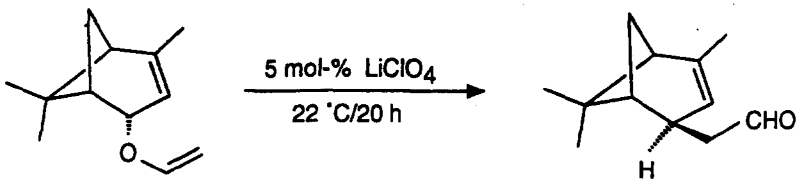


16 **17**

Finally, we discovered that catalytic amounts of $LiClO_4$ in CH_2Cl_2 induce the regioselective 1,3-Claisen rearrangement, processes that had previously been carried out using 5 M $LiClO_4$ in ether[1].



18 **19** (78%)



20 **21** (80%)

In summary, $LiClO_4$ suspended in CH_2Cl_2 is an efficient catalyst for Mukaiyama aldol additions, hetero-Diels-Alder reactions and 1,3-Claisen rearrangements, rate acceleration due to catalysis being enormous. The reaction conditions are mild, and workup is simple and safe. This means considerable progress in terms of efficiency, safety and environmental aspects relative to the traditional use of 5 M $LiClO_4$ in ether. In the case of classical Diels-Alder reactions, rate acceleration by the presence of catalytic amounts of $LiClO_4$ is rather moderate.

It is likely that in all of the reactions studied so far $LiClO_4$ behaves as a mild Lewis acid catalyst. In Diels-Alder reactions in 5 M $LiClO_4$/ether Grieco has postulated that this medium confines solute movement and hence retains solvent ordering, "compressing the reactants in much the same manner as the macroscopic application of external pressure"[1]. We do not believe that such effects are operating in our catalytic versions in CH_2Cl_2. In some cases the catalyst suspended in CH_2Cl_2 does not appear to dissolve to any appreciable extent, which may be an indication of heterogeneous catalysis[3]. However, in many cases studied here much or all of the $LiClO_4$ dissolves as the reaction proceeds. Mechanistic studies as well as the investigation of other $LiClO_4$-mediated reactions are underway.

EXPERIMENTAL SECTION

General Information: ^1H and ^{13}C NMR spectra were recorded on a Bruker AM 200 instrument. Mass spectra were recorded on a Varian MAT 311-DF instrument. GC studies were performed on a Siemens SiCHROMAT 1. All synthetic reactions were carried out under an atmosphere of argon. Syringes were dried and flushed with argon prior to use. Dichloromethane was dried by distillation from P_2O_5 and then CaH_2.

Typical $LiClO_4$ catalyzed Diels-Alder reaction:

Preparation of bicyclo[2.2.1]hept-5-en-2-carboxylic acid methylester (3/4)

To a solution of acrylic acid methylester (1 mmol, 86 mg) and cyclopentadiene (5 mmol, 330 mg) in CH_2Cl_2 (1 ml) is added lithium perchlorate (0.25 mmol, 25 mg) at -15°C. The mixture is stirred for 24 h before being poured on CH_2Cl_2 (15 ml). The mixture is washed with H_2O (2 x 15 ml), dried ($MgSO_4$) and immediately analyzed by GC. The chromatogram reveals 87% conversion based on acrylic acid methyl ester and an endo/exo ratio of 7.3 : 1.

$LiClO_4$ induced hetero-Diels-Alder reactions:

Preparation of 2,3-dihydro-2-phenyl-pyran-4-one (10)

To a solution of benzaldehyde (1 mmol, 106 mg) and E-1-methoxy-3-trimethylsiloxy-1,3-butadiene (2 mmol, 390 µl) in CH_2Cl_2 (2 ml) is added lithium perchlorate (0.09 mmol, 10 mg). The solution is stirred at room temperature for 23 h and then quenched with a dilute solution of sodium bicarbonate. The mixture is extracted with ether and the organic phase separated and dried ($MgSO_4$). After the solvent has been removed in vacuo CCl_4 (5 ml) and trifluoroacetic acid (50 µl) are added. The resulting solution is stirred for 15 min at room temperature. The solvent is removed in vacuo and the crude product purified by flash chromatography over SiO_2 (ether/pentane 40 : 60) to yield 122 mg (72%) of a colourless oil that is spectroscopically identical to an authentic sample of 2,3-dihydro-2-phenyl-pyran-4-one.

Preparation of 2-[(1'-benzyloxy)-ethyl]-2,3-dihydro-4H-pyran-4-one (12)

To a solution of 2-benzyloxypropanal (1 mmol, 164 mg) in CH_2Cl_2 (1 ml) is added E-1-methoxy-3-(trimethylsilyl)-1,3-butadiene (1.6 mmol, 300 µl) and lithium perchlorate (16 mg, 15 mol-%). The resulting mixture is stirred for 3 h at room temperature, washed with a saturated solution of sodium bicarbonate, dried ($MgSO_4$) and the solvent is removed in vacuo. The crude product is dissolved in 5 ml of ether. 1 ml of a 5 M solution of acetic acid in CH_2Cl_2 and 10 ml of water are added and the mixture is stirred at room temperature for 1 hour. The mixture is washed three times with 15 ml of water, dried ($MgSO_4$) and the solvent is removed in vacuo. The crude product is purified by column chromatography on SiO_2 (ether/pentane 70 : 30) to yield 170 mg of a colourless oil (73%) that is spectroscopically identical to an authentic sample of 2-[(1'-benzyloxy)-ethyl]-2,3-dihydro-4H-pyran-4-one.

Preparation of 2,3-dihydro-1-benzyl-2-phenyl-pyrid-4-one (17)

To a solution of benzylidene benzylamine (2 mmol, 390 mg) and E-1-methoxy-3-trimethylsiloxy-1,3-butadiene (4 mmol, 780 µl) in CH_2Cl_2 (2 ml) is added lithium perchlorate (0.38 mmol, 40 mg) and the resulting solution is stirred for 20 h at room temperature. The mixture is poured on CH_2Cl_2 (20 ml), washed with a saturated solution of sodium bicarbonate and dried ($MgSO_4$). The solvent is removed in vacuo and the crude product purified by flash chromatography (ether/pentane 90 : 10, then dichloromethane/triethylamine 95 : 5) to yield 280 mg (54%) of 2,3-dihydro-1-benzyl-2-phenyl-pyrid-4-one that is spectroscopically identical to an authentic sample.

Typical $LiClO_4$ induced [1,3] sigmatropic rearrangement of allyl vinyl ethers:
Preparation of 1-methyl-3-(formylmethyl)-cyclohexene (19)

To a solution of 1-methyl-3-vinyloxy-cyclohexene (1 mmol, 136 mg) in CH_2Cl_2 (1 ml) is added lithium perchlorate (0.06 mmol, 6 mg) and the mixture is stirred at room temperature for 10 h. The reaction mixture is poured on ether, washed with water (3 x 15 ml) and dried ($MgSO_4$). The solvent is removed in vacuo and the crude product purified by flash chromatography on SiO_2 (ether/pentane 7 : 93) to yield 106 mg (78%) of 1-methyl-3-(formylmethyl)-cyclohexene that is spectroscopically identical to an authentic sample.

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