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ACID CATALYZED INTRAMOLECULAR DIELS-ALDER REACTIONS IN LITHIUM PERCHLORATE-DIETHYL ETHER: ENHANCED REACTION RATES AND DIASTEREOSELECTIVITY

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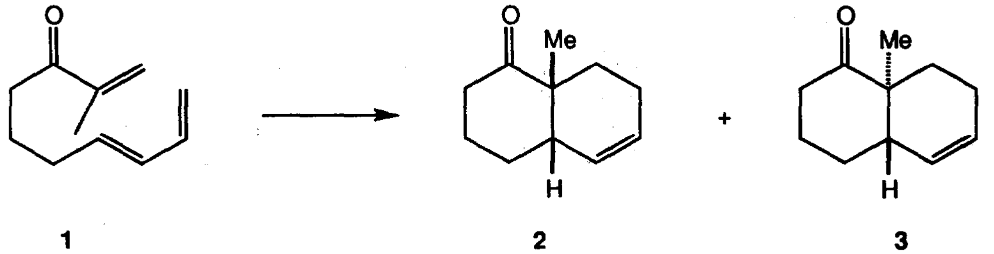
Abstract: The addition of 1.0-10 mol% of camphorsulfonic acid to 5.0 M lithium perchlorate in diethyl ether dramatically accelerates intramolecular Diels-Alder reactions and enhances the endo-exo selectivity.

Lithium perchlorate in diethyl ether has been shown to have a profound influence on the reaction rates of intermolecular Diels-Alder reactions[1] as well as on the diastereofacial selectivity which accompanies the [4+2] cycloaddition process.[2] We report that similar effects are observed for intramolecular Diels-Alder reactions[3] in 5.0 M lithium perchlorate-diethyl ether. In addition we report that these effects can be further accentuated by the use of catalytic acid in 5.0 M lithium perchlorate-diethyl ether.

Intramolecular Diels-Alder reactions of the type illustrated in Equation 1 are often conducted in hydrocarbon solvent at temperatures in excess of 100°C in a sealed tube.[3,4] Whereas the yields of cycloadducts obtained are good, the diastereoselectivity is modest. For example heating a 0.01 M solution of 1[5] in benzene at 120°C for 18 h provides a 72% yield of 2 and 3 in a ratio of 1.6:1.0. When 5.0 M lithium perchlorate in diethyl ether is employed as the medium, the reaction of 1 proceeds at ambient temperature over a 24 h period giving rise to a comparable yield of 2 and 3 with an improved diastereoselectivity of 3:1 (Table 1, compare entries 1 and 2). The intramolecular Diels-Alder reaction of 1 can be dramatically accelerated further by the addition of a few mol% of camphorsulfonic acid (0.5 M in tetrahydrofuran) to the



(1)

lithium perchlorate-diethyl ether medium (Table 1, entries 3 and 4). Most noteworthy is the increase in the ratio of the cis-fused cycloadduct **2** to the trans-fused product **3**.

It has been reported that lithium perchlorate suspended in methylene chloride[7] will catalyze Diels-Alder reactions. However, when a 0.05 M solution of **1** in methylene chloride was treated at ambient temperature with 30 mol% of solid lithium perchlorate, the isolated yield of **2** and **3** after 72 h was only 9% (Table 1, entry 5).[8] For comparison purposes, a conventional Lewis acid was examined.[4] Use of dimethylaluminum chloride necessitated very slow addition of the substrate to a solution of the Lewis acid in benzene (Table 1, entry 6) in order to avoid extensive decomposition. In summary, Table 1 reveals that in order to maximize the yield of **2**, the reaction of **1** is best performed in 5.0 M lithium perchlorate-diethyl ether containing 1.0-10 mol% of camphorsulfonic acid.

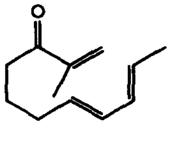
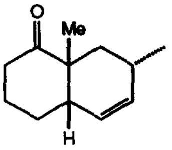
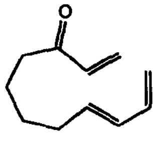
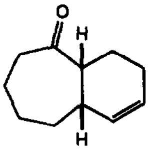
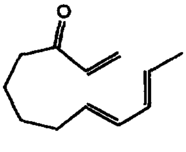
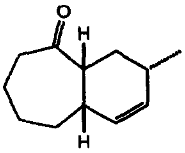
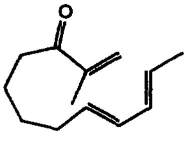
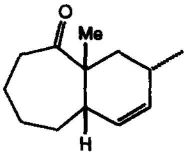
Table 1. Intramolecular Diels-Alder Reaction of Trienone 1[a]

entry	solvent	time, h	temp,°C	yield[b], %	ratio[c] cis:trans
1	benzene[d]	18	120	72	1.6:1
2	5.0 M $LiClO_4$-Et_2O	24	25	65	3.0:1
3	5.0 M $LiClO_4$-Et_2O 1.0 mol% CSA	1.5	25	88	4.5:1
4	5.0 M $LiClO_4$-Et_2O 10 mol% CSA	0.6	25	78	5.0:1
5	CH_2Cl_2 30 mol% $LiClO_4$	72	25	9[e]	2.4:1
6	0.1 M Me_2AlCl-benzene[f]	3	25	74	3.6:1

[a] All reactions were conducted 0.05 M in substrate 1 unless indicated otherwise. The CSA employed was 0.5 M in THF. [b] Isolated yields. [c] Ratios determined by ^1H NMR. [d] Reaction carried out 0.01 M in 1. [e] A 58% yield of recovered 1 was obtained. [f] A 0.02 M solution of 1 in benzene was added dropwise over a period of 2.5 h to a 0.1 M solution of Me_2AlCl in benzene.

Similar results were obtained with a number of other substrates (cf trienones **4-7**,[9] Table 2). For comparison purposes, data for the corresponding thermal reaction and reactions conducted in 5.0 M lithium perchlorate-diethyl ether, with or without added acid, is provided in Table 2. Note that in the case of substrate **7**, no reaction was observed in 5.0 M lithium perchlorate-diethyl ether. This is not surprising in view of the fact that the less demanding Diels-Alder substrate **6** proceeded very slowly in 5.0 M lithium

Table 2. Intramolecular Diels-Alder Reactions of Trienones 4-7[a]

substrate	solvent	temp,°C	time, h	major product	ratio[b] cis:trans	yield,[c] %
 4	benzene	120	20		1.3:1	92
	5.0 M LPDE	25	30		3.0:1	71
	5.0 M LPDE/CSA[d]	25	3.5		3.7:1	77
 5	benzene	140	15		2:1	84
	5.0 M LPDE	25	24		12:1	95
	5.0 M LPDE/CSA[e]	25	4		all cis	78
 6	benzene	180	19		1.3:1	87
	5.0 M LPDE	25	32		7:1	57[f]
	5.0 M LPDE/CSA[e]	25	4.5		44:1	88
 7	toluene	180	24		1.2:1	50
	5.0 M LPDE[g]	25	72		----	---
	5.0 M LPDE/CSA[h]	25	24		6:1	81

[a] All reactions in hydrocarbon solvent were conducted 0.01 M in substrate. All reactions performed in lithium perchlorate-diethyl ether (LPDE) were conducted 0.05 M in substrate. The camphorsulfonic acid (CSA) employed was 0.5 M in tetrahydrofuran. [b] Ratios determined by ^1H NMR. [c] Isolated yield. [d] 2.0 mol% CSA. [e] 1.0 mol% CSA. [f] Ca. 15% of the starting material was recovered. [g] No product was observed, ca. 90% of the starting trienone was recovered. [h] 10 mol% CSA.

perchlorate-diethyl ether. However, in the presence of 10 mol% of camphorsulfonic acid, the intramolecular Diels-Alder reaction of 7 proceeded smoothly at ambient temperature giving rise (81%) to a 6:1 ratio of cis- to trans-fused product. All of the acid catalyzed Diels-Alder reactions studied in 5.0 M lithium perchlorate-diethyl ether occurred with significantly improved diastereoselectivity.

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5. Prepared in straightforward fashion from 5,7-octadienal[6] by treatment with 2-propenyl magnesium bromide in tetrahydrofuran followed by PCC oxidation.
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8. We have examined a number of intramolecular Diels-Alder reactions in methylene chloride containing 1-30 mol% of lithium perchlorate and found that in the majority of cases studied reactions do not proceed to any appreciable extent (<10%) after 24 h at ambient temperature. (Unpublished work of S. T. Handy, Indiana University).
9. The substrates in Table 2 were prepared from the corresponding aldehydes[6] using either vinyl magnesium bromide or 2-propenyl magnesium bromide followed by oxidation with PCC or triphenylbismuth carbonate.[10]
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