

Synergistic<sup>†</sup> Catalysis of Anthrone  
Diels–Alder Reactions

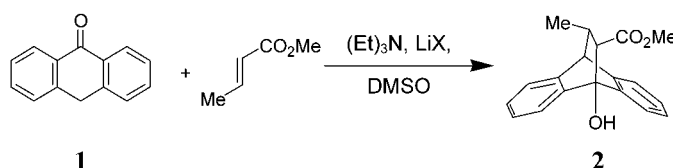
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## ABSTRACT



The combination of an amine base and Lewis acid ( $\text{Li}^+$ ) leads to synergistic catalysis of the Diels–Alder reaction of anthrone with methyl crotonate and some other less reactive dienophiles. These cycloadditions either do not occur with the individual catalysts used separately or they are greatly accelerated by the combined catalysts. DMSO solvent allows the use of LiCl as the Lewis acid source and can provide greater control of subsequent conversion to Michael adduct.

Bridgehead hydroxyl cycloadducts such as **3** have been shown to undergo facile base-induced retro-Diels–Alder reaction at or below room temperature (Figure 1).<sup>1</sup> This

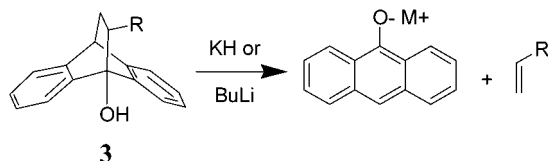


Figure 1. Generalized base-induced retro-Diels–Alder reaction.

synthetically useful procedure is driven by the formation of the phenoxide, and it benefits kinetically by accessing the oxyanion energy surface.<sup>2</sup>

<sup>†</sup> Synergy = working together; we have no evidence that bears on the possibility that the combined effect may be greater than the sum of the individual contributions of the two catalysts (an alternative definition).

(1) (a) Knapp, S.; Orna, R. M.; Rodrigues, K. E. *J. Am. Chem. Soc.* **1983**, *105*, 5494. (b) Nicolaou, K. C.; Bunnett, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1110.

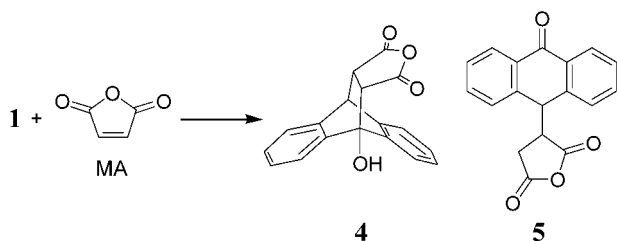
(2) (a) Rickborn, B. *Org. React.* **1998**, *52*, 1 (The Retro-Diels–Alder Reaction: Part I. C–C Dienophiles). (b) Wilson, S. R. *Org. React.* **1993**, *43*, 94 (Anion-Assisted Sigmatropic Rearrangements).

The adducts used to date in multistep syntheses have been formed by Diels–Alder reaction of O-protected anthracenols, with subsequent removal of the protecting group.<sup>1</sup> The modest diene reactivity of 9-RO-anthracenes limits the use of this approach to cycloadditions with very reactive dienophiles.

The possibility of forming bridgehead–OH adducts directly from anthrone (**1**) was recognized as early as 1934, although the attempted reaction with maleic anhydride (MA) at 188 °C led only to Michael adduct and to the incorrect conclusion that such Diels–Alder adducts could not be isolated.<sup>3</sup> Several years later it was shown that the Michael isomer is more stable than the Diels–Alder cycloadduct, but either isomer can be made to dominate by controlling the reaction time in refluxing HOAc (118 °C).<sup>4</sup> The choice of HOAc as solvent was intended to facilitate keto–enol tautomerism, but we find that the reaction of **1** with MA also affords, in nearly quantitative yields, Diels–Alder adduct **4** (2.0 h, refluxing toluene, 111 °C) or Michael adduct **5** (3.5 h, refluxing *m*-xylene, 139 °C) as shown in Figure 2. These observations support the view that the cycloaddition step, rather than tautomerism, is rate-determining. It was also

(3) Barnett, E. d. B.; Goodway, N. F.; Higgins, A. G.; Lawrence, C. A. *J. Chem. Soc.* **1934**, 1224.

(4) Cohen, D.; Millar, I. T.; Richards, K. E. *J. Chem. Soc. C* **1968**, 793.



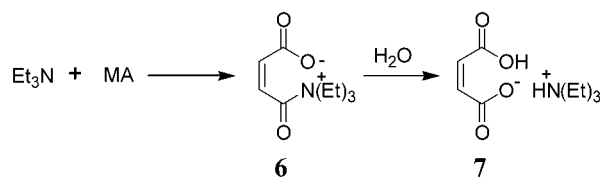
**Figure 2.** Cycloadduct and Michael adduct of anthrone + MA.

shown that the cycloadduct could serve as a precursor to Michael product under both acidic and “neutral” conditions.

Previous work from this laboratory demonstrated that anthrone in the presence of an amine can function as a very reactive diene in Diels–Alder reactions. Cycloadducts of dienophiles ranging in reactivity from *N*-methylmaleimide (NMM) through maleonitrile, fumaronitrile, dimethyl fumarate, methyl acrylate, to 2-butenolide at the least reactive end were all formed, stereo- and regiospecifically, in room temperature amine-catalyzed reactions.<sup>5</sup> This greatly enhanced reactivity is again attributed to accessing the oxyanion energy surface, with the notable difference that the weaker amine base allows the cycloadduct to be favored thermodynamically over the educts (compare Figure 1).

Several different cycloadducts were converted to the corresponding Michael products under amine-catalyzed conditions. With some substrates it proved difficult (or impossible) to avoid formation of Michael adduct, and the conversion of cycloadduct was especially facile in protic solvents such as methanol.<sup>5</sup> Additional evidence on the mechanism of this isomerization was obtained in the present study.

Conspicuously absent from the list of dienophiles that have been successfully employed under the amine-catalyzed conditions are MA and substituted acrylate analogues (e.g., crotonate). While the latter is rationalized simply on the basis of diminished reactivity, the failure of MA to give cycloadduct was initially puzzling. MA is very similar to (very reactive) NMM in cycloaddition rates with a wide range of dienes including anthracenes under neutral/acidic conditions.<sup>6</sup> The amine-catalyzed reaction of NMM with anthrone is rapid and efficient, leading to cycloadduct in quantitative yield within minutes. The failure of MA to give cycloadduct with anthrone under these conditions proved to be due to a very fast competing reaction of MA and the tertiary amine, which consumes the base. This reaction has been reported previously, as marked by intense color changes (charge transfer) and presumed formation of the acylammonium zwitterion **6** (Figure 3).<sup>7</sup> We believe that **6** is indeed formed, but as a very hygroscopic intermediate which absorbs water from the



**Figure 3.** Reaction of Et<sub>3</sub>N with MA and H<sub>2</sub>O.

surroundings to give triethylammonium maleate **7**. The details of the reaction steps remain unclear, but it appears that water is needed to generate color.<sup>8</sup>

In principle, the isomerization of a cycloadduct to a Michael product could occur as either an intra- or intermolecular process, the former being essentially a retro-aldol reaction. The intermolecular possibility requires a retro-Diels–Alder reaction, followed by a Michael reaction. The latter pathway appears to be ruled out by the observation that **4** is cleanly converted to **5** by prolonged amine-catalyzed treatment. If free MA had been generated, it would have been consumed by reaction with base.

No reaction of any kind was observed in several attempts to effect cycloaddition of anthrone with methyl crotonate under basic conditions. However, when LiClO<sub>4</sub> in ether was used in conjunction with Et<sub>3</sub>N, both cycloadducts and Michael adducts were formed. Neither catalyst was effective separately; thus a synergistic effect is observed.

The use of Lewis acids including Li<sup>+</sup> salts to catalyze Diels–Alder reactions is well-known. We assume that this is the fundamental role played by LiClO<sub>4</sub> as a component of the catalyst mixture, i.e., activation of the dienophile through cation coordination, although other possibilities may come into play including tethering of the reactants through coordination to the metal ion.

While higher concentrations of the salt cause more rapid reaction, the effect on rate is not directly proportional to concentration. The salt is clearly catalytic, since less than 1 equiv (per mole of either substrate or Et<sub>3</sub>N) leads to one of the better yields of cycloadduct **2**, as shown in Table 1.

The catalyst mixture also enhances the conversion of cycloadduct **2** to Michael product **8**. This secondary reaction can be largely avoided by the use of a lower concentration of LiClO<sub>4</sub> in ether, or through the use of DMSO solvent. DMSO as solvent has another advantage over Et<sub>2</sub>O in that LiCl can be used in place of LiClO<sub>4</sub> with no apparent loss in reactivity. Although concentrations of LiClO<sub>4</sub> in DMSO reach a maximum near 3.5 M, concentrations of approximately 1.5 M Li<sup>+</sup> in DMSO (and also in Et<sub>2</sub>O) appear to be optimal for synergistic catalysis, with no dramatic rate

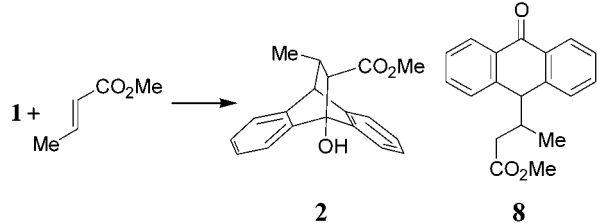
(5) (a) Rickborn, B.; Koerner, M. J. *Org. Chem.* **1989**, *54*, 6. (b) Rickborn, B.; Koerner, M. J. *Org. Chem.* **1990**, *55*, 2662. (c) Rickborn, B.; Koerner, M. J. *Org. Chem.* **1991**, *56*, 1373.

(6) Harrison, R.; Tobia, D.; Philips, B.; White, T.; DiMare, M.; Rickborn, B. *J. Org. Chem.* **1993**, *58*, 6701.

(7) Mayahi, M. F.; El-Bermani, M. F. *Can. J. Chem.* **1973**, *51*, 3539.

(8) When sublimed MA and Et<sub>3</sub>N are mixed in anhydrous ether in a closed system, color is not immediately observed. Upon exposure to (moist) air, the solution rapidly darkens, passing through various stages of yellow to intense brown as moisture diffuses through the solution. At higher concentrations, colorless **7** precipitates; this structure is supported by <sup>1</sup>H and <sup>13</sup>C NMR spectra, which exhibit the symmetry expected of rapid OH proton transfer, and by identity to material prepared by mixing maleic acid and Et<sub>3</sub>N.

**Table 1.** Reaction of Methyl Crotonate and Anthrone under Synergistic Catalysis

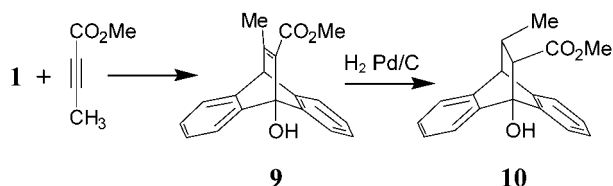


[LiX] <sup>b</sup>	[Et <sub>3</sub> N]	solvent	<i>t</i> (h)	% <b>2</b>	% <b>8</b>
0.07 <sup>a</sup>	1	Et <sub>2</sub> O	45	62	trace
1.25	0.25	Et <sub>2</sub> O	16	38	22
5.4	0.25	Et <sub>2</sub> O	0.5	15	0
5.4	1	Et <sub>2</sub> O	0.5	15	0
5.2	0.25	acetone	0.5	12	0
1.53	1	DMSO	16	71	0
1.52 <sup>c</sup>	1	DMSO	18	80	0

<sup>a</sup> [crotonate]<sub>init.</sub> = [anthrone]<sub>init.</sub> = ca. 0.25. <sup>b</sup> LiClO<sub>4</sub> unless otherwise noted. <sup>c</sup> LiCl.

increases noted for higher concentrations. Additionally, both LiClO<sub>4</sub> and LiCl show appreciable solubility in DMSO as hydrates,<sup>9</sup> which maintain catalytic reactivity for cycloaddition.

Synergistic catalysis also proved useful for methyl 2-butyrate cycloaddition to form **9**, a reaction that was otherwise sluggish at best. The reaction was carried out in ether at high (5.1 M) LiClO<sub>4</sub> concentration and halted after 3 h; **9** was isolated in 55% yield.<sup>10</sup> Hydrogenation of **9** quantitatively produced the formal (Z)-methyl 2-butyrate cycloadduct **10**, demonstrating a potentially useful approach to such cis-substituted materials (Figure 4).



**Figure 4.** Cycloaddition of methyl 2-butyrate and double bond reduction.

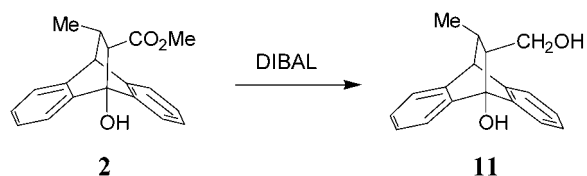
The further utility of free bridgehead hydroxyl cycloadducts in multistep syntheses remains to be examined. Since KH and also BuLi have been used to effect retro-Diels–

(9) LiCl is completely insoluble in Et<sub>2</sub>O; LiClO<sub>4</sub> is soluble in Et<sub>2</sub>O only when anhydrous.

(10) Equimolar amounts of reagents and Et<sub>3</sub>N were used. The course of the reaction was followed by NMR. It was stopped when bianthrone (air oxidation of anthrone) was detected.

Alder reactions under very mild conditions,<sup>1</sup> and amines can cause rearrangement to Michael adducts, many standard reaction conditions may prove difficult or impossible to apply. This question takes on special significance since in our experience the sterically hindered bridgehead hydroxyl does not react with most common protecting group reagents.

We chose reduction of the ester function as a demanding test of structural stability, using crotonate adduct **2** as the substrate. The “acidic” reducing agent DIBAL cleanly afforded the diol **11** (83%). More interestingly, the “basic” reducing agent LiAlH<sub>4</sub> worked equally well (85%), perhaps reflecting the formation and covalent nature of OAl (as opposed to OLi) bonds. Both reactions were carried out in 0.25 h at 0 °C, in ether. The ability to use these strong reducing agents without cleaving the bicyclic structure is encouraging (Figure 5).



**Figure 5.** Reduction of unprotected cycloadducts.

In conclusion, the utility of the base-catalyzed Diels–Alder reactions of anthrone has been extended to previously unreactive dienophiles through the addition of lithium salt cocatalysts. Since neither catalyst alone is effective with methyl crotonate, the effect is synergistic. The use of DMSO solvent and LiCl instead of LiClO<sub>4</sub> is noteworthy. Some further reactions of the cycloadducts illustrate a useful level of structural stability. Attempts to apply the mixed catalyst procedure to other substrates brought out limitations. Simple enones (cyclopentenone, cyclohexenone) do not react when either catalyst alone is employed but react rapidly under synergistic catalysis to give Michael adduct without evidence of cycloadduct intermediate. More highly substituted enones and unsaturated esters gave no reaction under any of the conditions explored. Substituted maleic anhydrides gave other processes, likely related to the reaction of MA described in this paper. No adducts could be isolated when quinones were employed as prospective dienophiles.

**Acknowledgment.** This work was supported in part by the UCSB Committee on Research.

**Supporting Information Available:** Experimental procedures and characterizations. <sup>1</sup>H NMR and <sup>13</sup>C NMR for **2**, **8** (ethyl ester), **9**, and **11** and <sup>1</sup>H NMR compound **10**. HiRes-MS available for compounds **2**, **9**, and **11**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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