

Dramatic Rate Accelerations of Diels–Alder Reactions in 5 M Lithium Perchlorate–Diethyl Ether: The Cantharidin Problem Reexamined

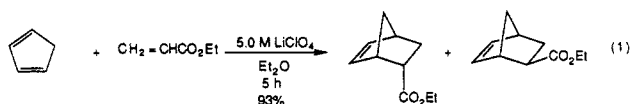
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During the past 15 years, studies on the Diels–Alder reaction¹ have produced dramatic results. The pronounced rate enhancements and improved stereoselectivities observed to date have been associated with cycloadditions conducted in (1) aqueous media² and (2) conventional organic solvents under ultrahigh pressure (8–20 kbar).³ While seemingly the result of two independent physical processes, it is most likely that there is a direct relationship between the rate acceleration observed when high pressure is applied to a Diels–Alder reaction and the rate enhancement observed in a solvent, like water, possessing a “high” internal solvent pressure.⁴ On the basis of this supposition, it seems logical to conclude that solvents (media) that possess internal solvent pressures equal to or greater than that of water should provide comparable rate accelerations for intermolecular cycloaddition processes. Herein, we report our findings, which show that 5.0 M lithium perchlorate in diethyl ether⁵ is a powerful medium for facilitating [4 + 2] cycloaddition reactions. *Diels–Alder adducts that hitherto were inaccessible via conventional means can now be realized through the agency of this remarkable medium.*

In a preliminary study, ethyl acrylate, dissolved in a 5.0 M solution of lithium perchlorate⁷ in diethyl ether, was treated with 1.0 equiv of cyclopentadiene (eq 1). After 5 h at ambient tem-



perature and pressure, a 93% isolated yield of cycloadducts possessing an endo:exo ratio of 8:1 was obtained. For comparison purposes, the reaction between cyclopentadiene and ethyl acrylate was conducted in water. After 5 h, a 73% yield of cycloadducts possessing an endo:exo ratio of 4:1 was obtained. The enhanced endo selectivity and reaction rate observed above in 5.0 M LiClO₄/Et₂O, coupled with the fact that the vast majority of organic compounds are insoluble in water and that water precludes the use of water-sensitive substrates, led us to explore further the potential of this unique solvent system for the Diels–Alder reaction.⁸

(1) Sauer, J.; Sustmann, R. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 799.
(2) For examples, see: (a) Rideout, D. C.; Breslow, R. *J. Am. Chem. Soc.* **1980**, *102*, 7816. (b) Grieco, P. A.; Garner, P.; He, Z. *Tetrahedron Lett.* **1983**, *24*, 1897. (c) Breslow, R.; Maitra, U.; Rideout, D. *Tetrahedron Lett.* **1983**, *24*, 1901. (d) Grieco, P. A.; Yoshida, K.; Garner, P. *J. Org. Chem.* **1983**, *48*, 3137.

(3) Dauben, W. G.; Kozikowski, A. P. *J. Am. Chem. Soc.* **1974**, *96*, 3664. Also, see: Van Eldik, R.; Asano, T.; Le Noble, W. J. *Chem. Rev.* **1989**, *89*, 549 and references cited therein.

(4) Cf.: McCabe, J. R.; Eckert, C. A. *Acc. Chem. Res.* **1974**, *7*, 251.

(5) Lithium perchlorate solutions in diethyl ether have previously been employed to accelerate reactions with polarized transition states.⁶ In contrast, the rates of intermolecular Diels–Alder reactions are essentially independent of solvent polarity, varying at most by 1 order of magnitude.

(6) Over 30 years ago, Winstein (Winstein, S.; Smith, S.; Darwish, D. J. *Am. Chem. Soc.* **1959**, *81*, 5511) observed that the ionization rate of *p*-methoxyneophyl *p*-toluenesulfonate in 0.1 M LiClO₄–Et₂O increased by a factor of 10³. Similarly, Pocker has reported (Pocker, Y.; Buchholz, R. F. *J. Am. Chem. Soc.* **1970**, *92*, 2075) that use of ca. 5.0 M LiClO₄–Et₂O increases the rate of ionization of trityl chloride by 7.0 × 10⁹.

(7) Commercially available (Aldrich) lithium perchlorate was dried under high vacuum (P₂O₅ trap) at 160 °C for 48 h. Lithium perchlorate is thermally stable at or above its melting point of 247 °C.

(8) In a recent study, Jaeger (Jaeger, D. A.; Tucker, E. C. *Tetrahedron Lett.* **1989**, *30*, 1785) observed that the fused salt ethylammonium nitrate gave endo selectivity enhancements for the Diels–Alder reaction between cyclopentadiene and methyl acrylate; however, the reaction rate was 1 order of magnitude slower than the corresponding reaction in water.

Table I. [4 + 2] Cycloadditions Employing 5.0 M Lithium Perchlorate in Diethyl Ether^a

entry	diene	dienophile	product	time	% yield ^b
1				3 h	90 ^c
2				15 min	80 ^d
3		MeO ₂ CC≡CCO ₂ Me		12 h	94 ^e
4		CH ₂ =C(OAc)CN		4 h	79 ^f
5				5 h	85 ^{g,h}
6		MeO ₂ CC≡CCO ₂ Me		24 h	68 ⁱ
7 ^j		CH ₂ =CHCO ₂ Me		5 h ^k	80 ^{l,m}
8 ^j		CH ₂ =CHCN		3 h ^k	78 ^{n,o}

^a All reactions were performed 1.0 M in diene and 0.2 M in dienophile unless stated otherwise. ^b Isolated yields. ^c Yield of 94% after 24 h at 60 °C (neat). ^d Yield of <20% after 24 h in water. ^e Yield of 50% after 12 h in water. ^f Yield of 27% after 24 h in water. ^g C(14)-βH:C(14)αH ratio equal 2.3:1. ^h Yield of 90% after 4.5 in water, employing the diene carboxylate. Use of the dienoic acid in water was slow. ⁱ Yield of 60% after 24 h in water. ^j 3.0 equivalents of diene were employed. ^k The reaction is worked up with methanol to cleave the imino ether. ^l Yield of 74% (endo:exo ratio 1:11.5) after 72 h in benzene at 60 °C. ^m An endo:exo ratio of 2.9:1 was observed in 5.0 M LiClO₄–Et₂O. ⁿ An endo:exo ratio of 1:3.7 was observed in 5.0 M LiClO₄–Et₂O. ^o Yield of 73% (endo:exo ratio of 1:9) after 48 h in benzene at 60 °C.

Table II. Reaction of Dienophile 1 with Furan at Ambient Temperature and Pressure in Varying Concentrations of Lithium Perchlorate in Diethyl Ether^a

molarity	% yield ^b	ratio (2:3) ^c
1.0	15	85:15
2.0	22	87:13
3.0	36	86:14
4.0	62	83:17
5.0	70	85:15

^a All reactions were run 0.5 M in dienophile for 9.5 h in the presence of 10 equiv of furan. ^b Isolated yields. ^c Ratios determined by ¹H NMR.

The procedure detailed above employing 5.0 M LiClO₄ in diethyl ether is applicable to a variety of substrates (Table I). Note that all reactions are homogeneous and were conducted at ambient temperature and pressure. All reactions exhibited pronounced rate accelerations and improved yields. In those cases involving water-sensitive substrates (entries 1, 7, and 8), reactions proceeded smoothly in excellent yield. For example, the [4 + 2] cycloaddition of the aza diene in entry 7 with methyl acrylate is complete after 5 h in 5.0 M LiClO₄/Et₂O, giving rise to an 80%

