

Catalysis of [2 + 2] Cycloadditions by 5 M Ethereal Lithium Perchlorate

Warunee Srisiri, Anne Buyle Padias, and H. K. Hall, Jr.*

C. S. Marvel Laboratories, Chemistry Department, The University of Arizona, Tucson, Arizona 85721

Received April 30, 1993

Summary: Lithium perchlorate (5 M) in ether reaction medium catalyzes cyclobutane formation.

Cyclobutanes are an important class of compounds, not only because they are included as the basic structure of some natural products but also because they can be converted to a variety of derivatives by further modifications such as ring enlargement and ring opening. For the construction of cyclobutane rings, the photochemical [2 + 2]-cycloaddition of olefins or the thermal stepwise [2 + 2]-cycloaddition between electrophilic olefins and nucleophilic olefins has generally been employed.

Ethereal lithium perchlorate has recently been recognized as an astounding medium for various reactions.¹ In 1986, Sauer had already recommended this polar reaction medium for the Diels-Alder reaction.² In 1990, Grieco et al. demonstrated that the Diels-Alder reaction of cyclopentadiene and ethyl acrylate proceeded with increased reaction rate and improved endo-selectivity in a 5 M solution of LiClO₄ in diethyl ether compared to an aqueous reaction medium.³ Grieco explained the accelerating effect of LiClO₄/ether in analogy to these aqueous systems, namely that the acceleration was due to better aggregation between the reaction partners owing to a hydrophobic effect or "internal pressure" on the reactants encapsulated in "solvent cavities". However, Dailey later showed that the Li⁺ ion is really functioning as a Lewis acid by complexing with the substituent on the dienophile.⁴ Ethereal LiClO₄ is superior to the aqueous medium due to its compatibility with substances sensitive to hydrolysis. Some reactions, which usually take place only under vigorous conditions, can occur smoothly under mild conditions at room temperature in this ethereal lithium perchlorate solvent. Examples are [4 + 3]-cycloadditions⁵ and 1,4-conjugate additions of silyl ketene acetals to α,β -unsaturated carbonyl compounds.⁶ In addition to this, using ethereal lithium perchlorate medium can totally change the reaction products. Alkyl vinyl ethers with lithium perchlorate undergo the unusual [1,3]-sigmatropic rearrangement, instead of the expected [3,3]-sigmatropic rearrangement, which is observed in aqueous ethanol.⁷

Lewis acids have been employed in a few instances to

catalyze [2 + 2]-cycloadditions,⁸ but the use of ethereal lithium perchlorate as solvent has not been reported to date for these cycloadditions. Huisgen has shown that 2 M ethereal LiClO₄ can be used to equilibrate the [2 + 2] cycloadducts of propenyl ethers and TCNE.⁹ In this study two series of previously impossible [2 + 2]-cycloadditions will be described in 5 M ethereal lithium perchlorate.

The first series of cycloadditions involves reaction of phenyl vinyl sulfide with olefins di- and trisubstituted with cyano and carbomethoxy groups. Olefins with two cyano groups on the same sp² carbon easily undergo [2 + 2]-cycloadditions with electron-rich olefins; for example, tetracyanoethylene¹⁰ or dimethyl 2,2-dicyanoethylenedicarboxylate¹¹ react with phenyl vinyl sulfide at room temperature to yield the expected cyclobutane in nearly quantitative yield. However, if an ester substituent is present at the most electronegative terminal carbon, inverse-electron-demand [4 + 2]-cycloaddition predominates. We have described this reaction previously; for example, the reaction of trimethyl ethylenetricarboxylate with methyl vinyl sulfide efficiently yields dimethyl 6-(methylthio)-3,4-dihydro-2H-pyran-4,5-dicarboxylate.¹² For three electrophilic olefins used in this study, namely dimethyl cyanofumarate (1), dimethyl 2-cyanoethylene-1,1-dicarboxylate (2), and trimethyl ethylenetricarboxylate (3), the same inverse-electron-demand [4 + 2]-cycloaddition is observed with phenyl vinyl sulfide in acetonitrile at room temperature, and no cyclobutane is formed.¹¹ The pyran formation is easily verified in the ¹H-NMR, due to the very distinguishable pattern for the thioacetal proton at δ 5.2. If the reaction of phenyl vinyl sulfide with olefins 1-3 or with methyl α -cyanoacrylate 4 is run in 5 M ethereal LiClO₄, efficient [2 + 2]-cycloaddition takes place at room temperature, as shown in Table I.¹³ The cyclobutanes are formed as mixtures of the 1,3-cis and -trans isomers, which are separated by column chromatography on silica gel. The isomer ratios are included in Table I. The two isomers can be identified by their distinct splitting pattern in ¹H-NMR: the cis isomer displays two sets of triplets for the protons on C₁ (carbon with SPh) and C₃ at δ 4.2 and 3.4 ppm, respectively, while for the less symmetric trans isomer a triplet is observed farther downfield (δ 4.8 ppm) for the proton on C₁. In every case the cis isomer is obtained as a solid, while the trans is an oil.

A second group of [2 + 2]-cycloadditions made possible by the use of 5 M ethereal LiClO₄ as solvent are reactions of rather non-nucleophilic donor olefins, such as styrene

(1) For recent reviews see: Grieco, P. A. *Aldrichimica Acta* 1991, 24, 61. Waldman, H. *Angew. Chem., Int. Ed. Engl.* 1991, 30, 1306.

(2) Braun, R.; Sauer, J. *Chem. Ber.* 1986, 119, 1269.

(3) Grieco, P. A.; Nunes, J. J.; Gaul, M. D. *J. Am. Chem. Soc.* 1990, 112, 4595.

(4) Forman, M. A.; Dailey, W. P. *J. Am. Chem. Soc.* 1991, 113, 2761.

(5) Fohlisch, B.; Krimmer, D.; Gerlach, E.; Kashammer, D. *Chem. Ber.* 1988, 121, 1585.

(6) Grieco, P. A.; Cooke, R. J.; Henry, K. J.; VanderRoert, J. M. *Tetrahedron Lett.* 1991, 32, 4668.

(7) Grieco, P. A.; Clark, J. D.; Jagoe, C. T. *J. Am. Chem. Soc.* 1991, 113, 5488.

(8) Padias, A. B.; Tien, T.; Hall, H. K., Jr. *J. Org. Chem.* 1991, 56, 5540. Johnson, C. R.; De Jong, R. L. *J. Org. Chem.* 1992, 57, 594. Takeda, T.; Fujit, T.; Morita, K.; Fujikawa, T. *Chem. Lett.* 1986, 1311. Hayashi, Y.; Nihata, S.; Narasaka, K. *Chem. Lett.* 1990, 2091. Baar, M. R.; Ballesteros, P.; Roberts, B. W. *Tetrahedron Lett.* 1986, 27, 2083. Yamazaki, S.; Fujitsuoka, H.; Yamabe, S. *J. Org. Chem.* 1992, 57, 5610. Clark, R. D.; Untch, K. G. *J. Org. Chem.* 1979, 44, 253. Engler, T. A.; Combrink, K. D.; Ray, J. E. *J. Am. Chem. Soc.* 1988, 110, 7931.

(9) Huisgen, R.; Graf, H. *J. Org. Chem.* 1979, 44, 2595. Huisgen, R.; Brueckner, R. *Tetrahedron Lett.* 1990, 31, 2553.

(10) Okuyama, T.; Nakada, M.; Toyoshima, K.; Fueno, T. *J. Org. Chem.* 1978, 43, 4546.

(11) Srisiri, W. Ph.D. Thesis, The University of Arizona, 1993.

(12) Hall, H. K., Jr.; Rasoul, H. A. A.; Gillard, M.; Abdalkader, M.; Noguez, P.; Sentman, R. C. *Tetrahedron Lett.* 1982, 23, 603.

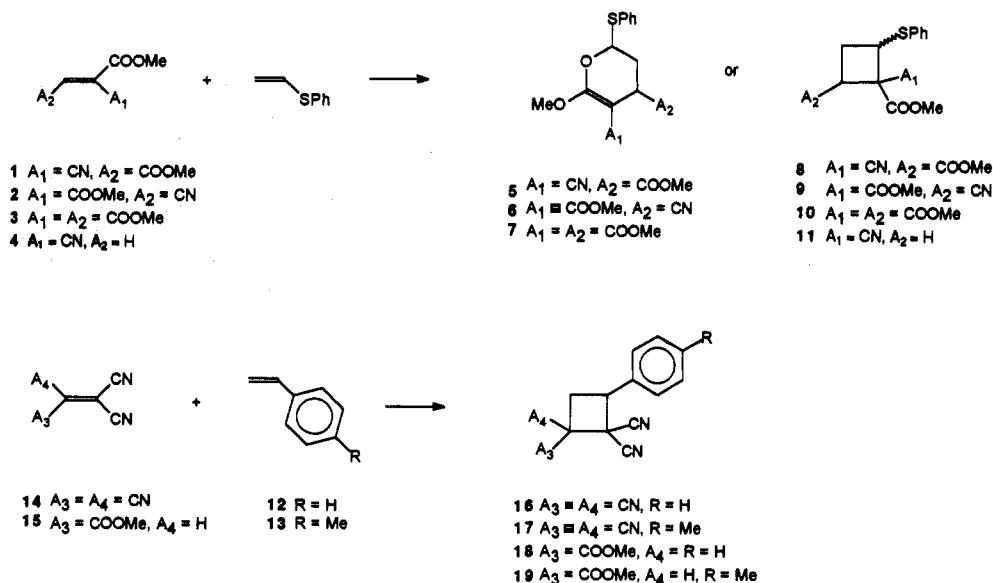
(13) Cyclobutane 8 could also be obtained by reaction of phenyl vinyl sulfide with dimethyl cyanofumarate at reflux in acetonitrile, but the isomer ratio was different (cis/trans 80/20 for LiClO₄/ether versus 43/57 for the thermal reaction).

Table I. Comparison of the Cycloaddition Reactions of Olefins Pairs in Acetonitrile and in 5 M LiClO₄ in Ether

nucleophilic olefin	electrophilic olefin	acetonitrile		5 M ethereal LiClO ₄ ^c	
		product	% yield ^a	cyclobutane	% yield ^d (cis/trans ratio)
phenyl vinylsulfide	1	pyran 5	70	8	75 (80/20)
	2	pyran 6	80	9	85 (80/20)
	3	pyran 7	100	10	72 (50/50)
	4	no rctn		11	83 (67/33)
styrene (12)	14	no rctn		16	67
	15	no rctn		18	40 (85/15) ^e
<i>p</i> -methylstyrene (13)	14	17	50 ^b	17	72
	15	no rctn		19	34 (50/40)

^a Yields of pyran adducts determined by NMR spectroscopy after 20 h at 25 °C. ^b Reaction conditions: acetonitrile, 25 °C, 4 days. ^c Reaction conditions: 25 °C, 20 h. ^d Isolated yields. ^e Reaction run in the presence of 10 mol % TEMPO.

Scheme I



and *p*-methylstyrene, with the highly electrophilic olefins tetracyanoethylene TCNE 14 and methyl 3,3-dicyanoacrylate MDA 15. With the more electron-rich olefins *p*-methoxystyrene¹⁴ and isobutyl vinyl ether,¹⁵ TCNE undergoes very efficient [2 + 2]-cycloaddition. According to the literature, TCNE and styrene only react at high pressure to give a rather unstable 1:1 Diels-Alder adduct.¹⁶ With *p*-methylstyrene, TCNE does form a cyclobutane adduct, but the reaction takes 4 days at room temperature. MDA 15 does not react with either styrene or *p*-methylstyrene at room temperature. In these four cases 5 M ethereal LiClO₄ as reaction medium makes the cyclobutane formation possible, as shown in Scheme I and Table I. In the case of styrene with 15, however, spontaneous copolymerization predominates over cyclobutane formation. However, in the presence of a nitroxide free radical inhibitor, 2,2,6,6-tetramethylpiperidinoxyl radical (TEMPO), the desired cyclobutane 2,2-dicyano-3-carbomethoxy-1-phenylcyclobutane (18) was obtained in 40% yield. The

novel cyclobutane adducts could be purified by recrystallization and were fully characterized. The proton α to the phenyl group appears as a clearly distinguishable doublet of doublets in the NMR spectrum: at δ 4.6 for styrene adducts and δ 4.0 for *p*-methylstyrene.

In this paper we have described the utility of 5 M LiClO₄ in ether reaction medium to obtain [2 + 2]-cycloadditions. The full details of this study, including the effect of other Lewis acids on these cycloadditions, will be described in a full paper at a later date.

Acknowledgment. The authors gratefully acknowledge partial financial support by the National Science Foundation, Division of Materials Research, and Dr. R. Bates for help with the interpretation of the NMR spectra. W.S. is grateful for the financial support provided by "The Anantamahidol Scholarship" sponsored by the King of Thailand.

Supplementary Material Available: Typical experimental procedures and NMR data (7 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(14) Williams, J. K.; Wiley, D. W.; McKusick, B. C. *J. Am. Chem. Soc.* 1962, 84, 2210.

(15) Huisgen, R. *Acc. Chem. Res.* 1977, 10, 117, 199.

(16) Uosaki, Y.; Nakahara, M.; Osugi, J. *Bull. Chem. Soc. Jpn.* 1981, 54, 3681.