

1-1-2002

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KACAN, MESUT and KARABULUT, H. R. FERHAT (2002) "Diels-Alder Reactions Using 5 M LiClO₄ -Diethyl Ether Catalyst," *Turkish Journal of Chemistry*. Vol. 26: No. 2, Article 14. Available at: <https://journals.tubitak.gov.tr/chem/vol26/iss2/14>

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Diels-Alder Reactions Using 5 M LiClO₄-Diethyl Ether Catalyst

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Received 29.03.2001

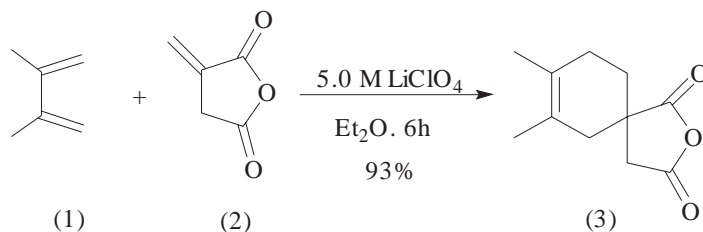
The rate acceleration of Diels-Alder reactions in 5.0 M lithium perchlorate-diethyl ether was re-examined using itaconic anhydride and itaconic acid. Rate acceleration was observed for non-functionalised dienes, but functionalised dienes gave the starting or polymeric materials.

Introduction

The derivatives of arylacetic acid and arylpropionic acid have become increasingly important drugs as these compounds are highly effective anti-inflammatory agents and have less serious side-effects than such drugs as *ibufenac*¹ and *alclofenac*² or the more complex *pirprofen*³.


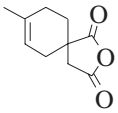

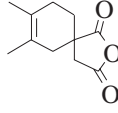
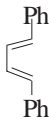
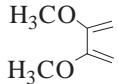


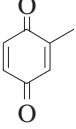
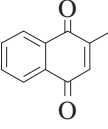
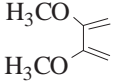
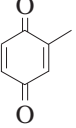
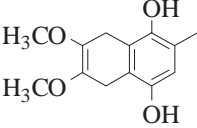
In 1980, in a projected new approach to arylacetic acid synthesis, Fletcher attempted to obtain phenylacetic acid and its derivatives by Diels-Alder (D-A) reactions using mainly itaconic acid and itaconic anhydride as the dienophile⁴. Unfortunately, a low yield (28-56%) was obtained in most of these reactions.

In 1990, Grieco et al. reported a new catalytic version of the Diels-Alder reaction using 5.0 M lithium perchlorate-diethyl ether (LPDE)⁵ at ambient temperature and pressure and they obtained high yields in a number of D-A reactions. According to Grieco et al., the effect of the LPDE medium was to create a high internal solvent pressure. In the present study, the LPDE solvent system was re-examined in different dienes and dienophiles at ambient temperature and pressure. In a preliminary study, itaconic anhydride (2) was dissolved in a 5.0 M LPDE in diethyl ether solution and treated with 1.0 eq. of 2,3-dimethyl-1,3-butadiene (1). After 6 h at ambient temperature and pressure, a 93% isolated yield (3) of cycloadduct was obtained.



The same procedure was then applied to the Diels-Alder reactions of a variety of dienes with itaconic anhydride or 2-methylbenzoquinone as dienophile (Table 1). All reactions were homogeneous and were conducted at ambient temperature and pressure.

Table 1. [4+2] Cycloaddition Employing 5.0 M LPDE

Entry	Diene	Dienophile	Product	Time	Yield % ^c
1		IA	 (4)	6h	96
2		IA	 (5)	5h	93
3		IA	SM	12h	—
4		IA	b	6h	—
5		IA	b	6h	—
6			 (6)	5h	90
7			 (7)	5h	89

^aAll reactions were performed with 1.0 M in diene and 0.2 M dienophile unless stated otherwise. ^bPolymeric materials. ^cIsolated yields. IA: Itaconic anhydride SM: Starting material.

Experimental

Preparation of 5.0 M lithiumperchlorate-diethylether (LPDE): Anhydrous LiClO₄ was recrystallised twice from distilled water in the form LiClO₄·H₂O and finally dried at 160°C (0.5 mmHg) for at least 48 h. In a 100 ml volumetric flask, the solvent-salt solution was prepared by first weighing in the necessary amount of lithiumperchlorate (53.2 g, 0.5 mol). The flask was filled with the required solvent (anhydrous diethylether) and the contents were stirred for 2 h at 20°C⁶. The 5.0 M LPDE solution was kept in a closed flask and used with a syringe for the reactions.

The general reaction of diene with dieneophile: A mixture of diene (25 mmol), dienophile (5 mmol) and 5.0 M LPDE solution (5 ml) was stirred at ambient temperature and pressure for 4 h. Water (20 ml) was added to the reaction mixture and extracted with diethylether (3 x 25 ml), and the solvent was evaporated under reduced pressure to give the crude product. All of the obtained products are known compounds except (7) and the crude products were purified by crystallisation or distillation. The pure products were compared (mp, bp, IR, ¹H NMR) with genuine samples prepared independently.

Cycloaddition reaction of 2-methyl-1,3-butadiene with itaconic anhydrite (4): To a solution of 5.0 M LPDE (5 ml), 2-methyl-1,3-butadiene (1.7 g, 25 mmol) and itaconic anhydrite (0.56 g, 5 mmol) were reacted at ambient temperature and pressure for 6 h, according to the general procedure. When the reaction was completed, water (20 ml) was added to the reaction mixture and then extracted with diethylether. The solid crude product was purified by column chromatography to give 0.81 g (96%) of 4-carboxy-4-carboxymethyl-1-methyl-cyclohexene (4) as colourless crystals. Mp: 126-128°C (lit⁷., 127-128°C); ν_{max} (nujol mull) 1720, 1780 cm⁻¹ (C=O); δ ¹H 1.72 (3H, s, CH₃), 1.94-2.22 (6H, m, ring protons), 2.8 (2H, s, CH₂O), 5.4 (1H, t, vinyl H); Anal. Calc. for C₁₀H₁₂O₃: C, 66.66; H, 6.66. Found: C, 66.72; H: 6.62.

Cyclisation reaction of 2,3-dimethyl-1,3-butadiene with IA (5): A mixture of 2,3-dimethyl-1,3-butadiene (1.8 g, 25 mmol) itaconic anhydride (0.56 g, 5 mmol) and 5.0 M LPDE solution (5 ml) was stirred at ambient temperature and pressure for 5 h according to the general procedure. After the work up the solvent was evaporated under reduced pressure to give the crude colourless solid product. The crude product was purified by column chromatography [silica gel: petroleum ether (bp 40-60)/diethylether (3:1)] and 0.9g (93%) of pure 4-carboxy-4-carboxymethyl-1,2-dimethyl-cyclohexene (5) was obtained as colourless crystals. Mp: 102-104°C (lit⁷., 102.5-105°C); ν_{max} (nujol mull) 1710, 1780 cm⁻¹ (C=O); δ ¹H 1.64 (6H, s, 2xCH₃), 1.7-2.3 (6H, m, ring protons), 2.75 (2H, s, CH₂O), 5.4 (1H, t, vinyl H); Anal. Calc. for C₁₁H₁₄O₃: C, 68.04; H, 7.21. Found: C, 68.21; H, 7.24.

Cycloaddition reaction at 1-acetoxy-1,3-butadiene with 2-methyl-1,4-benzoquinone (6): 1-acetoxy-1,3-butadiene (1.68 g, 25 mmol) and methyl-1,4-benzoquinone (0.36 g, 0.3 mmol) were reacted in the presence of 5.0 M LPDE solution (15 ml) according to the usual procedure. After 5 h stirring at room temperature the reaction mixture was quenched with water and extracted with diethylether (3x30 ml). The organic phase was evaporated under reduced pressure. The crude residue was recrystallised from ethanol to give 0.48 g (89%) of 2-methyl-4,4-naphthoquinone (6) as bright yellow crystals, mp. 104-106°C (lit⁸., 104-105°C); ν_{max} (nujol mull) 1680 cm⁻¹ (C=O); δ ¹H 2.2 (3H, s, CH₃), 7.6-8.2 (4H, m, arom.), 6.8 (1H, m, vinyl H); Anal. Calc. for C₁₁H₈O₂: C, 76.74; H, 4.65. Found: C, 76.81; H, 4.58.

Cycloaddition of 2,3-dimethoxy-1,3-butadiene with 2-methyl-1,4-benzoquinone (7): To a 5.0 M solution of LPDE (15 ml), the diene (1.68 g, 15 mmol) and the dienophile were added and the reaction mixture was stirred for 5 h according to the general procedure. The reaction mixture was worked up and the crude product was purified by column chromatography [silica gel: petroleum ether (bp 40-60)/diethylether (2:3)] to give 0.65g (89%) the novel compound of 5,8-dihydro-6,7-dimethoxy-4,4-naphthalenediol (7) as a colourless product. Mp:143-145°C; ν_{max} (nujol mull) 2450-3500 cm⁻¹ (br., -OH); δ ¹H (d₆-acetone) 2.12 (3H, s, CH₃), 3.36 (4H, s, ring protons), 3.6 (6H, s, OCH₃), 6.4 (2H, br, OH), 7.42 (1H, s, arom); Anal. Calc. for C₁₃H₁₆O₄: C, 66.10; H, 6.77. Found: C, 66.23; H, 6.76.

Results and Discussion

The initial report by Grieco et al. on the effect of 5.0 M lithium perchlorate-diethyl ether on the rate and yield of a number of Diels-Alder reactions was extremely stimulating⁵. Reactions that formerly required high temperature or high pressure for success could now be performed at ambient temperature and ambient pressure. We were intrigued by the interesting suggestion that the source of this effect was due to the very high “internal pressure” of 5.0 M LPDE solution. In the present study, rate accelerations were observed for a number of reactions, especially for non-functionalised dienes, but functionalised dienes gave the starting or polymeric materials, except a few reactions with 2-methylbenzoquinone as a used dieneophile. If rate enhancement was due to a “pressure” effect caused by the lithium perchlorate-diethyl ether solution as postulated by Grieco et al.⁵, then in principle the rates of all Diels-Alder reactions should have been increased in this medium. However, for most reactions studied here, large rate enhancements were not observed. An alternative explanation for Grieco et al.’s results may be simply that the rate acceleration of the D-A reactions in the lithium perchlorate-diethyl ether medium was due to Lewis acid catalysis.

Acknowledgement

Mesut Kacan is grateful to the University of Trakya, Edirne, for financial support.

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