

Aqueous Diels-Alder methodology toward some selected monoterpenes

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As part of our project involving the development of synthetic protocols utilizing aqueous reaction conditions, some naturally occurring terpenes have been synthesized in our laboratory. Limonene, α -terpineol, and terpinolene were indirectly prepared via aqueous Diels-Alder reaction. The Diels-Alder reactions were carried out in water alone as medium without Lewis acid catalysis to afford the intermediates that are subsequently transformed to the target compounds by conventional means.

Keywords: monoterpenes; aqueous Diels-Alder reaction; cycloaddition

INTRODUCTION

Numerous synthetic strategies and methodologies had been employed to synthesize a myriad of compounds since the advent of the art of synthetic organic chemistry. Naturally occurring molecules, as well as designed ones, have each succumbed to the unrelenting quest of the organic chemist to synthesize them.

Among the naturally occurring compounds are the terpenes. Terpenes are natural unsaturated hydrocarbons derived from isoprene units [1]. An examination of their molecular structure reveals that, in general, the carbon skeletons are built theoretically by the union of two or more isoprene or isopentane residues. Terpenes that contain atoms other than hydrogen and carbon are classed as terpenoids [2]. There are many ways by which terpenes can be obtained, the most common of which is isolation from essential oils of plants.

Virtually, all monoterpenes have been prepared synthetically. Examples of monoterpenes are carvone, camphor, menthol, limonene, terpineol, and terpinolene, just to name a few. These monoterpenes are important for they serve as necessary ingre-

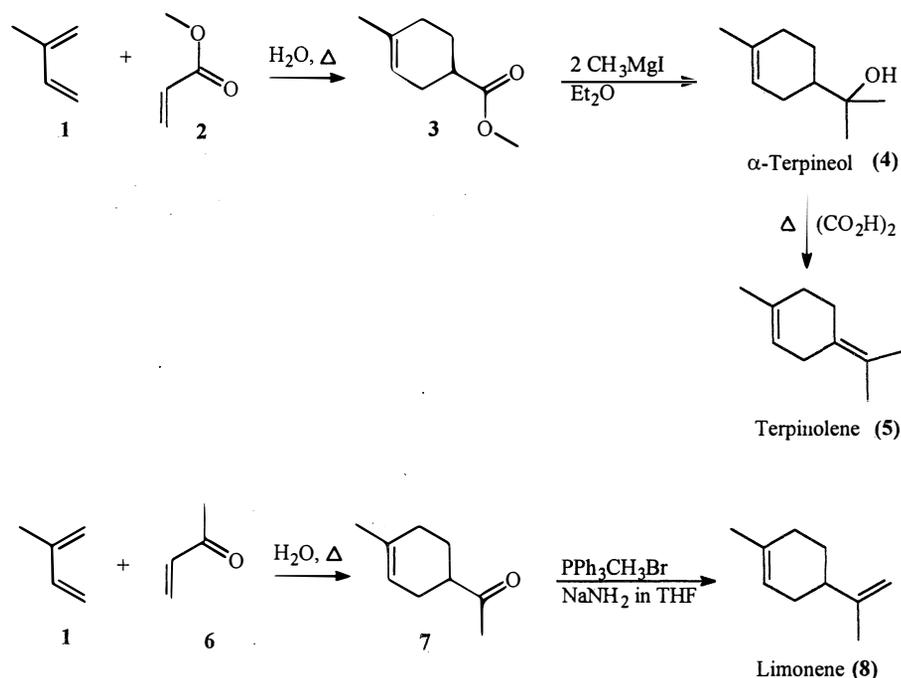
dients or raw materials in the pharmaceutical, cosmetic and chemical industry. Limonene, for one thing, is used as cleaning and solvent agent in many industries.

In one way or another, these monoterpenes have been prepared by conventional means. The methodologies, though elegant by themselves, are conventional in the aspect that they employ organic solvents as media to facilitate the reaction. These solvents, such as benzene, chloroform, toluene, and dichloromethane are toxic and pose environmental hazards.

This paper exemplifies a deviation from conventionality and it is in accordance with the general trend of redefining organic synthesis by developing synthetic protocols and techniques that are more environmentally friendly.

We report here the syntheses of three monoterpenes that involve aqueous Diels-Alder conditions. One of the most striking features of the aqueous Diels-Alder reaction is the speed by which the reaction proceeds. The enhanced rate of reaction compared to the conventional one is attributed to solvent effects. These effects are hydrophobic interactions and hydrogen bonding [3-6]. The work presented here, which capitalizes on the obvious advantage of the nature of the aqueous Diels-Al-

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Scheme 1. Routes toward the preparation of cyclic monoterpenes via aqueous Diels-Alder reaction as key step.

der mode mentioned, describes the method of synthesizing terpinolene, terpineol and limonene. Our synthetic approach is presented in Scheme 1.

EXPERIMENTAL

General procedure. IR spectra were recorded on Bio-Rad FT-IR spectrophotometer 40-A using NaCl as reference. Wavenumbers are expressed as reciprocal centimeters (cm^{-1}). The $^1\text{H-NMR}$ spectra were recorded using JEOL Lambda 400 NMR Spectrometer. Chemical shifts are expressed in ppm units (δ) relative to TMS standard. Reactions were monitored via thin layer chromatography (TLC) using UV illumination, iodine, or immersion in 10% H_2SO_4 in EtOH as visualization techniques. The solvents used were either AR or HPLC grade. The water used was deionized distilled water. Isoprene (Aldrich), methyl vinyl ketone (Sigma), and methyl acrylate (Sigma), were used without further purification. Methyl magnesium bromide (Aldrich), methyl triphenyl phosphonium bromide (Aldrich), and sodium amide (Across) were used as is.

METHODOLOGY

4-Methylcyclohex-3-ene-1-carboxylic acid methyl ester (3) and 1-acetyl-4-methylcyclohex-3-ene (7). A mixture of water (200 mL), isoprene (**1**) (60 mL, 0.88 mol), and methyl acrylate (**2**) (25 mL, 0.40 mol) or methyl vinyl ketone (**6**) (25 mL, 0.40 mol) in a tightly capped 500 mL round bottom flask equipped with a magnetic stirring bar was heated at 80°C for 3 h. After

cooling, the top organic layer was collected. The excess unreacted reagents in the organic layer were separated by distillation. The residue was washed twice with 50 mL brine, 50 mL water, and finally dried with anhydrous MgSO_4 . The product obtained is a very slightly yellow oily liquid with a sweet smell.

Yield for 4-methylcyclohex-3-ene-1-carboxylic acid methyl ester (**3**) is 88%. IR (film): 2929, 2842, 1738, 1437, 1379, 1307, 1256, 1225, 1169 cm^{-1} ; $^1\text{H-NMR}$ (CDCl_3) (400 MHz): δ (ppm) = 5.28 (s, 1H), 3.6 (s, 3H), 2.7–1.65 (m, 7H), 1.63 (s, 3H).

Yield for 1-acetyl-4-methylcyclohex-3-ene (**7**) is 95%. IR (film): 2965, 2926, 1712, 1441, 1377 cm^{-1} ; $^1\text{H-NMR}$ (CDCl_3) (400 MHz): δ (ppm) = 5.28 (s, 1H), 2.10 (dd, $J = 2.4, 12$ Hz, 2H), 1.94 (m, 1H), 1.77 (s, 3H), 1.71 (m, 2H), 1.68 (t, 2H), 1.55 (s, 3H).

Terpineol (4). A dry 125-mL, two-necked round bottom flask equipped with a magnetic bar was fitted with a reflux condenser with drying tube. After flushing with nitrogen gas for several minutes, an ether solution of methyl magnesium bromide (40 mL, 3.0 M) and methyl acrylate-isoprene adduct (**3**) (6.7 g, 44 mmol) were introduced to the flask via cannula. The resulting mixture was refluxed for 1.5 h after which saturated ammonium chloride was added to quench the reaction. The mixture was then extracted with diethyl ether (2×20 mL). The combined ethereal extract was washed with brine (2×5 mL), and finally with water (10 mL). The dried extract was then dried over anhydrous MgSO_4 . Evaporation of the solvent yielded a very slightly yellow oily, liquid residue. Silica gel column chro-

Table 1. Comparison of Diels-Alder reactions conducted under various conditions.

Diene (Entry Number)	Dienophile (Entry Number)	Reaction Medium	Reaction Temperature (°C)	% Yield
1	2	H ₂ O	80	85
	2	Methanol	reflux	67
	2	Benzene	reflux	4
	6	H ₂ O	80	80
	6	H ₂ O	30	52
	6	CHCl ₃	80	11
	6	CHCl ₃	30	6

Note: All reactions were carried out for 3 h and the amounts of reagents and solvents for the control runs (using organic solvent) are the same with the aqueous runs.

matography of the dried residue using acetone as eluent afforded terpineol as a sweet smelling clear oil (Yield = 95%). IR (film): 3385, 2969, 2838, 1441, 1338 cm⁻¹; ¹H-NMR (CDCl₃) (400 MHz): δ (ppm) = 5.3 (s, 1H), 2.22–1.5 (m, 8H), 1.6 (s, 3H), 1.13 (s, 6H).

Terpinolene (5). A mixture of terpineol (**4**) (1.0 g, 6.49 mmol) and saturated solution of oxalic acid (10 mL) was refluxed at the boiling point of water for 30 min after which the reflux set-up was converted to a distillation set-up. The mixture was then distilled. The organic layer of the two-layer distillate was separated, collected, and subsequently dried over MgSO₄. Silica gel column chromatography of the dried distillate using acetone as eluent afforded terpinolene as a menthol-smelling clear colorless oil (Yield = 84%). IR (film): 2970, 2937, 1450, 1366 cm⁻¹; ¹H-NMR (CDCl₃) (400 MHz): δ (ppm) = 4.7 (s, 1H), 3.5 (s, 2H), 2.7 (s, 3H), 1.9 (m, 7H), 1.8 (d, J = 2.3 Hz, 2H), 1.6 (s, 4H), 1.5 (s, 3H).

Limonene (8). In a glove box, sodium amide (2.6 g, 66 mol) and methyltriphenylphosphonium bromide (22 g, 61 mmol) was charged to a two-necked, 125 mL round bottom flask with a condenser fitted with drying tube. Freshly distilled tetrahydrofuran (35 mL) was then introduced. The resulting mixture was stirred for 20 min after which methyl vinyl ketone-isoprene adduct (**7**) (8.5 g, 61 mmol) was added via syringe. Stirring was continued for another 1.5 h. The reaction was then quenched with 25% sodium hydroxide. The resulting mixture was then partially acidified with 25% hydrochloric acid after which it was extracted with diethyl ether (2 × 15 mL). The ether extract was dried over MgSO₄ and evaporated to afford a yellow oily residue. Chromatography of the residue using basic activated alumina and 9:1 petroleum ether (40–60°C) as eluent afforded limonene as a clear sweet smelling oil (Yield = 88%). IR (film): 2965, 2929, 1437, 1376 cm⁻¹; ¹H-NMR (CDCl₃) (400 MHz): δ (ppm) = 5.3 (s, 1H), 4.6 (s, 2H), 2.7 (s, 3H), 1.9 (m, 7H), 1.8 (d, J = 2.3 Hz, 2H), 1.6 (s, 4H), 1.5 (s, 3H).

DISCUSSION

The results of cycloaddition of isoprene with the respective dienophiles run in aqueous media are presented in Table 1. Presented also are the results of trial runs carried out in organic solvents such as methanol, benzene, and chloroform. These runs were conducted to compare the efficiencies of each medium in facilitating the pertinent Diels-Alder reactions and to affirm the existing claim that aqueous Diels-Alder reactions are generally faster and high yielding.

The Diels-Alder reaction of isoprene with **6** is much high yielding compared with **2**. This is due to the fact the methyl moiety of **6** is more electron releasing than the methoxy group in **2**. These electronic effects were observed in our previous work dealing with the aqueous DA reaction of isoprene and naphthoquinone [7].

The overall yield for the synthesis of terpinolene, utilizing **3** and **7** as key intermediates respectively, (3 steps) is 70% while that for limonene (2 steps) is 84%. This clearly indicates that the aqueous Diels-Alder route to yield the subsequent products is superior, in terms of yield, compared to the conventional methodologies available [8–10]. Also, in terms of economic and environmental considerations, our protocol surpasses the conventional ones. The temperature at which the aqueous DA reaction was carried out was found to be the optimum temperature. This is very much lower compared to the same reaction carried out in xylene. Likewise, the need for distillation to remove the organic solvent was eliminated.

Our protocol further affirms claims in the literature that aqueous media play a role regarding the regiochemistry of some reactions. The stereochemical effects of the media used in this study have not been investigated due to the conclusion of some groups that the medium has no marked influence on the course of the reaction [5]. This influence implies that the medium cannot be involved in the transition state.

CONCLUSION

The high yielding nature of aqueous Diels-Alder reaction for the construction of cyclic monoterpene intermediates described here proved to be a viable alternative route towards the preparation of other commercially important monoterpenes. Comparison of aqueous Diels-Alder with those carried out in conventional organic solvents indeed showed that water is a potent medium for synthesizing terpene intermediates.

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