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CYCLOPRPAN FORMATION VERSUS SIGMATROPIC REARRANGE PRODUCTS IN ETHYLDIAZACETATE ADDITION TO ALLYLTHIOTETRAPYRAN

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ABSTRACT

During the course of our investigation to the synthesis of 2-(2'-tetrahydropyranyl thio) methyl-1-carboxycyclopropane through the cyclic addition of 2-allythiotetropyran with ethyldiazoacetate results in cyclopropane derivatives in cis and trans form in addition to sigmatropic rearrangement of 1,3 and 1,5 shift were obtained. Conformation of the structure of cyclopropane, sigmatropic rearrange products is confirmed through elemental analysis, IR, NMR and MP. The mechanisms of sigmatropic arrangement are discussed.

KEYWORDS: Cyclic addition, Ethyldiazoacetate, Sigmatropic rearrangement, Cyclopropane, Temperature effects.

1. INTRODUCTION

Ionizing radiation comprises any electromagnetic or particulate radiation capable of producing ions, directly or indirectly, in its passage through matter. Among the many types of ionizing radiation available to nuclear physicists, only a limited number have been employed in radiobiological studies and protection experiments. These include X-rays, gamma-rays and neutrons.[1-4] Owing to the growing application of nuclear energy for peaceful purposes the study of chemical protection has attracted increasing interest and today this rapidly expanding field has resulted in the development of a special branch of biochemical pharmacology and medicinal chemistry.[5-11] The available evidence indicates that chemical protection against

ionizing radiation is brought about by a reduction in the immediate chemical and biochemical lesion.[12] The mechanism of chemical protection is therefore intimately connected with the mechanism of radiobiological damage and the problems can profitably be discussed together. It is therefore necessary to consider briefly some aspects of radio physics, radio chemistry and mammalian radiobiology.

In the course of our investigation to synthesize cis and trans (2-methylmercaptocyclopropylamine) to differentiate between possible mechanism of radiation protective agents. These cis and trans rigid structures are related to eclipsed and staggered conformation of δ-mercaptopropylamine. Doherty's proposal[3] suggests that the cis isomers should exhibit greater radiation protection than the trans isomer. Alternatively Ormered and Alexander's proposal suggests stereochemistry to have little effect on biological activity.[13-14]

If the trans isomer of 2-methylmercaptocyclopropylamine turns out to be the more active isomer, this may suggest "the disulfide hypothesis" is the applicable mechanism.[1,3,15]

In this paper, we would like to report an interesting sigmatropic rearrangement that we encounter during the synthesis of cis and trans 2-(2'-tetrahydropyranylthio) methyl-1-carboethoxycyclopropane.

2. MATERIALS AND METHODS

2.1. Instrumental

Chemical methods

Melting points were determined by using a calibrated Thomas-Hoover melting apparatus. IR spectra were recorded using a Perkin-Elmer 257 spectrophotometer, ^{1}H-NMR spectra were acquired with the aid of Varian 300 MHz spectrometer and DMSO-d_6 as solvent and TMS as standard (Jordan University). Microanalyses were performed at oil exploring company, Baghdad, Iraq. The results obtained had a maximum deviation of ± 0.4% of the theoretical value.

2.2. Experimental

2-Allyl thio tetrahydropyran (**2**)

Allyl mercaptan, 1.74 (0.1 mol) and 200 mg of p-toluene sulfonic acid (which served as a catalyst) were placed in 500 ml RB-flask fitted with a reflux condenser and magnetic stirrer. Dihydropyran (2.84 g, 0.1 mol) was added drop wise. The reaction mixture was heated on

stem bath. After heating for 5-10 minutes, a vigorous exothermic reaction started and continued during the addition of dihydropyran. After 90 minutes, the refluxing was stopped and potassium carbonate (1.0 g) was added. The mixture was stirred at room temperature for 1 hour, filtered and fractionally distilled yielding 80.2 g (50%) of 2-allyl thiotetrahydropyran (**2**) B.p. 42-44 (0.1 mm): infrared (neat, cm^{-1}) showed bands at 3080 ($C=CH_2$, stretch), 2940, 2860, 2850 (CH_2, stretch) 1635 (C=C, stretch), 1180, 1080, 1040, 1015 (tetrahydropyranyl group) and 940 ($S-CH_2$). ^{1}H-NMR (d-chloroform, δ) 2.18-1.28 (broad, multiplet, 6H $(CH_2)_3$, 3.20 (multiplet, 2H, $S-CH_2$), 3.5 (multiplet, 2H, $C-CH_2$). The vinyl protons appear as multiplets overlapping with ($O-CH_2-S$) at 5.20 (multiplet, 3H, $C=CH_2$, O-CH-S) and 5.82 (multiplet, 1H, C=CH).

Analysis: Calcd. For $C_8H_{14}OS$: C, 60.71; H, 8.91; S, 20.25 found C, 60.63; H, 8.85; S, 20.47.

2(2'-tetrahydropyranylthiomethyl-1-carboxy-cyclopropan and Ethyl-α-ally-(2-tetrahydropyranylthio)-acetate

In a 250 ml three-necked flask provided with a reflux condenser, dropping funnel and magnetic stirrer was placed 2-allyl thiotetrahydropyran (3.15 g, 0.1 mol) and 50 mg of copper powder. The mixture was stirred rapidly, heated at 160-164^{o}C (oil bath) and the ethyldiazoacetate (11.4 g, 0.1 mol) was added at such a rate so as to avoid a vigorous reaction. After ethyl diazoacetate addition, the evolution of nitrogen ceased. The reaction mixture was refluxed for 2 hours filtered and fractionally distilled affording 8.2 g of low boiling distillated (40-60^{o}C at 0.2 mm). The distillate was analyzed by gas liquid partition chromatography. These products were tentatively identified as diethyl maleate, diethyl fumarate.

Ethyl-α-allyl- α-(2-tetra hydropyranyl thio)-acetate (**4**)

B.p. 72-74^{o}C at 0.015 mm, was identified by infrared and NMR spectra.

The IR spectrum (neat, cm-1) showed bonds at 3080 ($C=CH_2$, stretch), 2940, 2860, 2850 (CH_2, stretch), 1735 (C=O, stretch) 1649 (C=C), 1080, 1050, and 1020 (CH_2, tetrahydropyranyl group), 940 possibly $S-CH_2$ ^{1}H-NMR (d-chloroform, δ), 1.25 (triplet, 3H, CH_3, J=2.2 Hz), 1.45 to 2.0 (broad, multiplet, 6H, $(CH_2)_3$) of tetrahydropyranyl, 2.57 (multiplet, 2H, $S-CH_2$), 3.5 (multiplet, 2H, β, CHO- S-CH-COOEt) of the tetrahydropyranyl group, 4.0 (multiplet, 3H, α-CHO-$COOCH_2$), 4.16 (multiplet, (S-CH-COOEt), 1H, CH=C), 5.70 (multiplet, 2H, C==CH_2).

Analysis Calcd for $C_{12}H_{20}O_3S$, C,58.98; H, 8.25; S, 13.12. Found, C,58.74; H, 8.15; S, 13.25.

And the second product was

2-(2'-tetrahydropyranyl thiomethyl-1-carboethoxy-cyclopropane (3)

The structural identification of (3) as follow

5.5 g (22.5%) (**3**), was obtained as a colorless liquid, B.p. 120-122^{o}C (0.2 mm). gas liquid partition chromatography on 3.8% silicon gunrubber (UC-W 98) on chromosorb-W (80-100 mesh) 4 ft 0.25 in glass column with column temperature 190, injection part temperature 320, detector temperature 280, inlet pressure of 40 psi and carrier gas (He), flow rate of (60 ml/cm) showed two peaks at 3.2 minutes (87%) trans (**3a**) and 4.0 minutes 13% cis (**3b**) mixture of (**3a**) and (**3b**) and infrared spectrum (neat, stretch), 1720 (C=C stretch), 1105, 1080, 1040, 1015 (tetrahydropyranyl group and cyclopropane absorption), ^{1}H-NMR (d-chloroform, δ) 0.9-1.2 (multiplet, 2H, CH_2,) of cyclopripane, 1.34 (triplet, 3H, CH_3, J=2.2 Hz,), 1.4-2.15 (multiplet, 7H, $(CH_2)_3$, α-CH), 3.3 (multiplet, 1H, CH-cyclopropane α-to COOEt); 3.56 (multiplet, 1H, α-CHO); 4.14 (quartet, 2H, CH2, J=2.2 Hz, of the ester group); 5.0 (multiplet, 1H, O-CH-S); 5.2(doublet CH_2-S, J=2.2 Hz,).

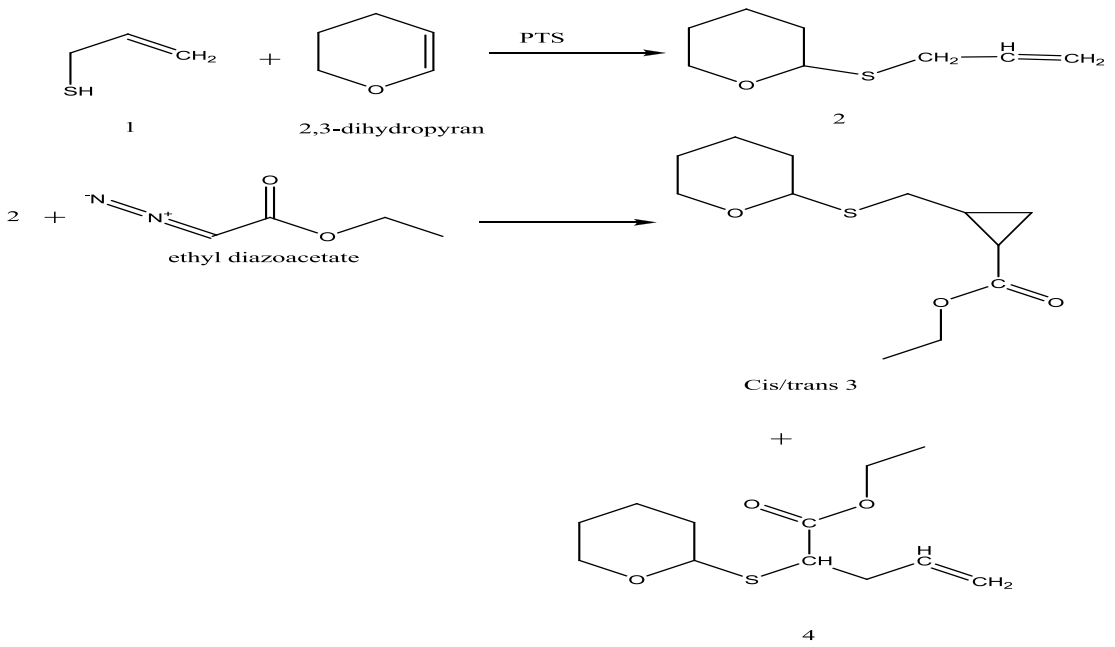
Analysis Calcd for $C_{12}H_{20}O_3S$: C, 58.98; H, 8.25; S, 13.13. Found: C, 58.74; H, 8. 15; S, 13.50.

3. RESULTS AND DISCUSSION

Allylmercaptan (**1**) served as a starting material and was readily converted to 2-allyl thiotetrahydropyran (**2**). The reaction of (**1**) with 2,3-dihydropyran in the presence of p-toluene sulfonic acid as catalyst, afforded (**2**) in 80% yield. The elemental analysis, infrared and NMR spectra were consistent with the assigned structure (**2**). Reaction of 2-allyl thio tetrahydropyran (**2**) with ethyldiazoacetate afforded a mixture of cis and trans 2-(2'-tetrahydropyranyl thio)methyl-1-carboethoxycyclopropane (**3**) in 71.4% yield. When the reaction was run at 150-155^{o}C and Cu powder was employed as catalysts, 38.6% of the sulfonium ylide rearrangement product (**4**) was also obtained. The relative ratio of cyclopropylester (**3**) relative to rearranged product (**4**) is dependent upon the reaction temperature. Product ratio analysis using GLPC at various reaction temperatures is listed in table 1.

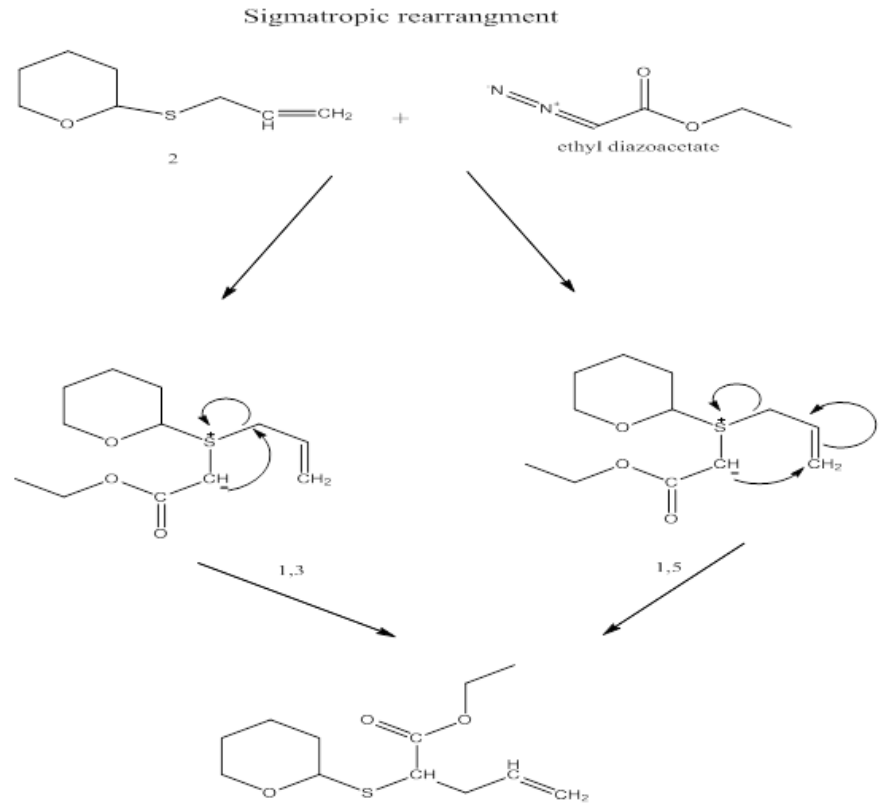
It is well known that ethyl diazoacetate reacts with thiols and thioethers to form sulfonium ylides **4.**[16-18] Such sulfonium ylides are known to undergo the Stenven's rearrangement; which depending upon the structure of the ylides, may either involve an antrafacial 1,3-sigmatropic rearrangement or 1,5 suprafacial sigmatropic rearrangement.[19, 20] Although one

cannot exclude any competing formation of product involving a 1,3-sigmatropic rearrangement process.[19, 20] In our case, both the 1,3 and 1, 5-rearrangements would afford the same compound. Since it is well known that the sulfonium ylide formation is a reversible process[20]; we studied the reaction at various temperatures in order to increase the yield of the desired cyclopropane (relative to the Steven's rearrangement product). This objective in fact is realized in table (1). The most favorable condition relative to sulfonium ylide formation was at 120-125^{o}C. The poorest relative yield formation was at 180-185^{o}C. For preparative purpose a temperature of 160-165^{o}C was found to be the most desirable. At 180^{o}C other side reaction products were detected by GLPC and polymer formation increased. Most other byproducts of the reaction are low boiling materials resulting from dimerization and trimerization of ethyl diazoacetate or unreacted started olefine. These materials are easily removed by distillation under reduced pressure affording a residual oil, which upon further distillation (120-122^{o}C) at 0.2 mm affords cis and trans 2-(2'-tetrahydropyranyl-thio) methyl-1-carboethoxycyclopropane (**3**) in an isomeric ratio trans to cis 83:17. This isomeric ratio is based on gas chromatography analysis. It was expected that the trans isomers would have shorter retention time.[17]



Scheme 1

Synthesis of 2(2'-tetrahydropyranyl)thiomethyl-1-carboxycyclopropan (3) and ethyl-α-(2-tetrahydropyranylthio)acetate (4).



Scheme 2

The mechanism for sigmatropic rearrange product.

Table 1: Gas chromatographic analysis of the products of (3) and (4) resulting from the reaction of 2-allylthiotetrahydropyran (2) and ethyldiazoacetate at various temperatures.

Temperature	Yield of cyclopropane (3)[a] ± 0.5%	The yield of the rearranged Sulfonium ylide (4) ± 0.5%
120-125	21.5	78.5
140-145	50.9	49.1
150-155	71.4	38.6
160-165	83.3	16.7
180-185	91.4	8.6

[a]:calculation is based on (**3**) and (**4**) (detected gas chromatographically) equal to 100%. The absolute yield of cyclopropane at 160-165^{o}C = 83.3%; the yield at 180-185^{o}C = 91.4%; the absolute yield of rearranged product (**4**) at 160-165^{o}C = 16.7; the yield at 180-185^{o}C = 8.6%.

CONFLICT OF INTERESTS

Declared None.

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