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PREPARATION AND DIELS-ALDER REACTIONS OF SOME FUNCTIONALIZED ISOPRENES

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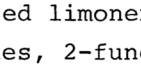
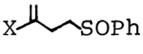
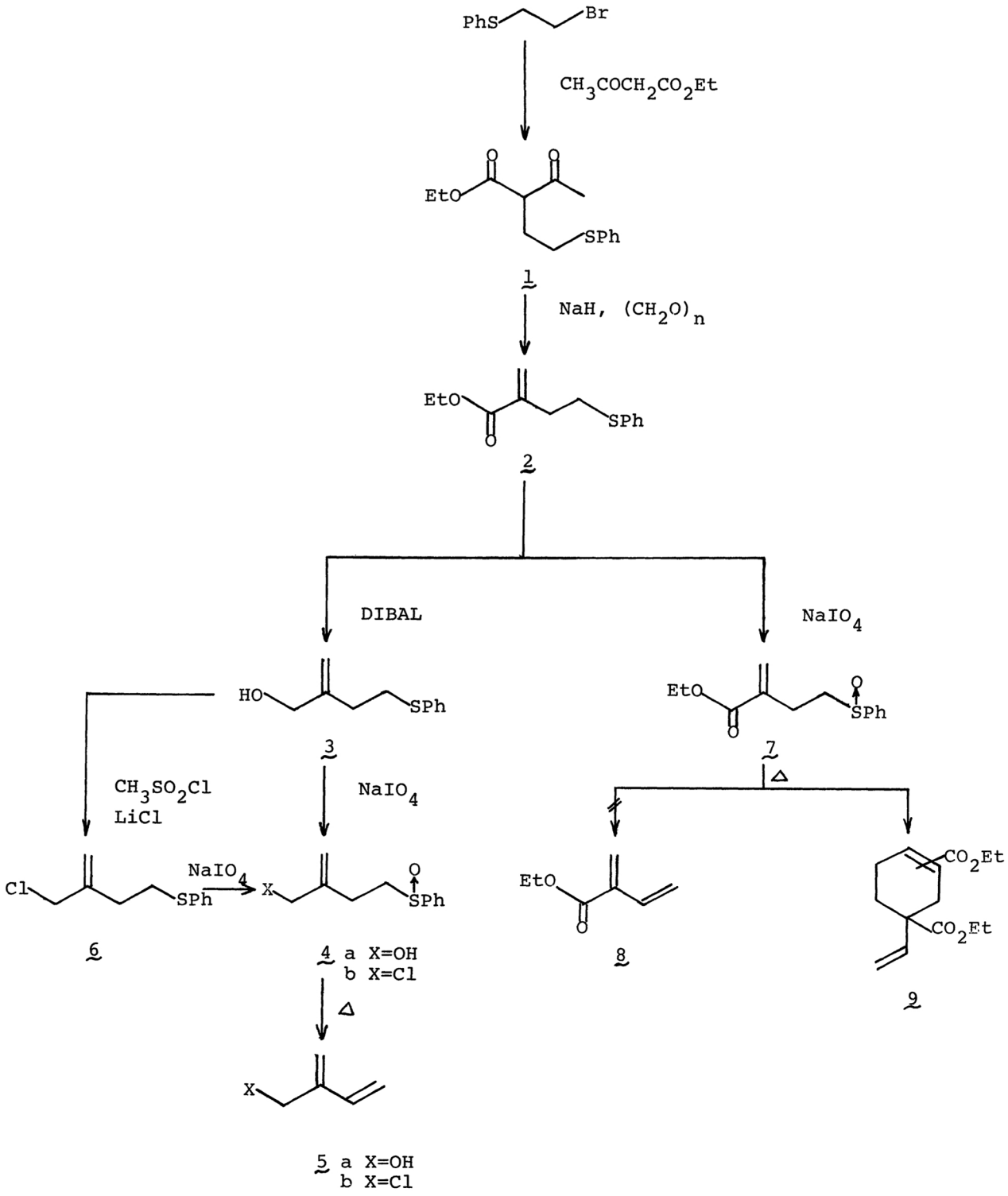
A convenient synthetic method for some functionalized isoprenes employing 1-bromo-2-phenylthioethane and ethyl acetoacetate as starting materials is reported. It has also been found that the dienes thus obtained gave functionalized limonene analogs by Diels-Alder reaction with methyl vinyl ketone.

Substitution of the methyl group of isoprene by a functional group seems to provide versatile applications to terpenoid syntheses. However, only a few studies have been made on the preparation of functionalized isoprenes. For example, by thermolysis of halides of isoprene/SO_2 adduct, 2-halomethyl-1,3-butadienes were obtained in ca. 10 % yields,[1,2] and the bromomethyl compound has been converted to the 2-hydroxymethyl derivative.[3] Recently, it was reported that the coupling reaction of the trimethylsilylmethyl Grignard reagent and chloroprene gives 2-trimethylsilylmethyl-1,3-butadiene.[4]

Here, we wish to present preliminary results on the development of a convenient synthetic method for functionalized isoprenes employing readily available starting materials. In addition, Diels-Alder reactions of these dienes resulting in the formation of functionalized limonene analogs are also reported.

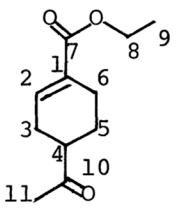
For the desired dienes, 2-functionalized-4-phenylsulfinyl-1-butene,  , can be a good precursor. Although some derivatives (X = CO_2Et, CH_2OH, and CH_2Cl) have been obtained, their preparation is tedious.[5] We have found a much simpler route leading to these compounds. That is, ethyl acetoacetate was treated with 1-bromo-2-phenylthioethane to give the alkylated compound 1, which was successfully converted to the α-methylenated ester 2 according to the method reported by Ueno et al..[6] The ester thus obtained was oxidized to  . The overall sequence of our method is depicted in the Scheme and actual procedures are briefly illustrated as follows. Reaction of 1-bromo-2-phenylthioethane (0.857 mol) with ethyl acetoacetate (1.54 mol) in the presence of K_2CO_3 (1.45 mol) and KI (0.438 mol) in acetone yielded the alkylated compound 1 (yield; 82 % based on 1-bromo-2-phenylthioethane). The alkylated compound 1 (80.8 mmol) was treated with sodium hydride (5.04 g) in THF, and then addition of paraformaldehyde (12.0 g) to this solution followed by heating under reflux for 4 hr gave the α-methylenated ester 2 (yield; 90 %). Reduction of the ester 2 with DIBAL provided the hydroxymethyl compound 3 (yield; 85 %). The compound 3 was treated with excess $NaIO_4$ to afford the sulfoxide 4a, thermolysis of which in the presence of $NaHCO_3$ at 150° C gave 2-hydroxymethyl-1,3-butadiene (5a) (yield; 63 %).

Scheme

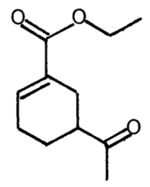

PhS
Br
$CH_3COCH_2CO_2Et$
EtO
SPh
1
NaH, $(CH_2O)_n$
2
DIBAL
$NaIO_4$
HO
3
CH_3SO_2Cl
LiCl
$NaIO_4$
Cl
X
6
4 a X=OH
b X=Cl
Δ
5 a X=OH
b X=Cl
7
8
9
CO_2Et

The overall yield based on 1-bromo-2-phenylthioethane is ca. 40 %. Reaction of the hydroxymethyl compound 3 with CH_3SO_2Cl and excess LiCl yielded the chloromethyl compound 6, which was converted to 2-chloromethyl-1,3-butadiene (5b) according to the procedures shown in the Scheme (overall yield; 33 %).

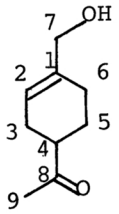
When thermolysis of the sulfoxide of carbethoxy derivative 7 was conducted as a neat form or in xylene, no expected diene 8 was detected, but the Diels-Alder reaction product 9* was obtained. Formation of the carbethoxy diene 8 was proved by thermolysis of the sulfoxide in the presence of excess methyl vinly ketone in xylene for 4 hr. The Diels-Alder reaction product 10 was formed in this reaction (yield; 72 % based on 7). The hydroxymethyl derivative 11 was obtained in 85 % yield by the reaction of the diene 5a with excess methyl vinyl ketone in refluxing xylene for 4 hr. GLC analysis of these adducts showed a single peak, but their ^{13}C NMR spectra showed two pairs of signals for C_1 and C_2 carbons, respectively, indicating that these adducts are mixtures of 4- and 5-acetyl derivatives (ca. 4:1 ratio). Comparison of these spectra with those of authentic specimens prepared from perillaldehyde[7] revealed that the major products were 4-acetyl derivatives (10a and 11a).



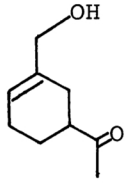
10a



10b



11a



11b

In summary, we believe that the method described herein is much more convenient than those reported so far, and further studies on preparations and applications of these dienes are now in progress.

NMR and IR Data

1) NMR (CCl_4) δ 1.15 (t, 3H, CH_3, J=7 Hz), 1.85-2.30 (m, 2H, CH_2, J=7 Hz), 2.10 (s, 3H, CH_3CO), 2.85 (t, 2H, CH_2S, J=7 Hz), 3.10 (t, 1H, COCHCO, J=7 Hz), 4.50 (q, 2H, OCH_2, J=7 Hz), 6.90-7.40 (m, 5H, aromatic); IR (film) 1735, 1710, 1625,1585 cm^{-1}.

2) NMR (CCl_4) δ 1.25 (t, 3H, CH_3, J=7 Hz), 2.05 (t, 2H, allylic, J=7 Hz), 3.00 (t, 2H, CH_2S, J=7 Hz), 4.12 (q, 2H, OCH_2, J=7 Hz), 5.50 (s, 1H, olefinic), 6.10 (s, 1H, olefinic), 6.90-7.40 (m, 5H, aromatic); IR (film) 1710, 1625, 1595 cm^{-1}.

3) NMR (CCl_4) δ 2.28 (t, 2H, allylic, J=8 Hz), 2.95 (t, 2H, CH_2S, J=8 Hz), 3.25 (bs, 1H, OH), 3.90 (s, 2H, CH_2O), 4.78 (s, 1H, olefinic), 4.95 (s, 1H, olefinic), 6.80-7.40 (m, 5H, aromatic); IR (film) 3350, 1650, 1595 cm^{-1}.

4a) NMR ($CDCl_3$) δ 2.28-2.60 (m, 2H, allylic), 2.70-3.10 (m, 2H, CH_2SO), 3.95 (s, 2H, CH_2O), 4.35 (bs, 1H, OH), 4.79 (s, 1H, olefinic), 5.00 (s, 1H, olefinic), 7.20-7.90 (m, 5H, aromatic).

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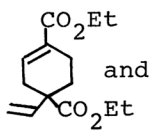
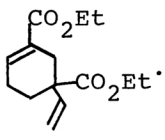
*GC-MS analysis showed that the product is a mixture of isomers,  and  .

4b) NMR ($CDCl_3$) δ 2.30-2.70 (m, 2H, allylic), 2.80-3.10 (m, 2H, CH_2SO), 4.00 (s, 2H, CH_2Cl), 4.98 (s, 1H, olefinic), 5.17 (s, 1H, olefinic), 7.15-7.90 (m, 5H, aromatic).

5a) NMR (CCl_4) δ 3.85 (bs, 1H, OH), 4.18 (s, 2H, CH_2O), 4.80-5.40 (m, 4H, olefinic), 6.10- 6.60 (m, 1H, olefinic); IR (film) 3350, 1595 cm^{-1}.

5b) NMR (CCl_4) δ 4.13 (s, 2H, CH_2Cl), 5.00-5.50 (m, 4H, olefinic), 6.05-6.60 (m, 1H, olefinic); IR (film) 1595 cm^{-1}.

6) NMR (CCl_4) δ 2.45 (t, 2H, allylic, J=7 Hz), 3.00 (t, 2H, CH_2S, J=7 Hz), 3.95 (s, 2H, CH_2Cl), 4.93 (s, 1H, olefinic), 5.10 (s, 1H, olefinic), 6.90-7.35 (m, 5H, aromatic).

7) NMR ($CDCl_3$) δ 1.24 (t, 3H, CH_3, J=7 Hz), 2.35-2.75 (m, 2H, allylic), 2.75-3.20 (m, 2H, CH_2S), 4.10 (q, 2H, OCH_2, J=7 Hz), 5.68 (s, 1H, olefinic), 6.08 (s, 1H, olefinic), 7.10-7.90 (m, 5H, aromatic); IR (film) 1713, 1635 cm^{-1}.

9) NMR (CCl_4) δ 1.20 (t, 3H, CH_3), 1.25 (t, 3H, CH_3), 1.60-2.50 (m, 6H, CH_2, allylic), 4.07 (q, 2H, OCH_2), 4.08-5.20 (m, 2H, olefinic), 5.60-6.10 (m, 1H, olefinic), 6.80 (m, 1H, CH=CCO).

10) NMR (CCl_4) δ 1.25 (t, 3H, CH_3, J=7 Hz), 1.70-2.70 (m, 7H, CHCO, CH_2, allylic), 2.13 (s, 3H, CH_3CO), 4.10 (q, 2H, OCH_2, J=7 Hz), 6.85 (m, 1H, CH=CCO).
^{13}C NMR ($CDCl_3$) δ 210.7 (C_{10}), 167.1 (C_7), 138.8 (C_2 of 10b), 137.7 (C_2 of 10a), 130.2 (C_1 of 10a), 129.3 (C_1 of 10b), 60.4 (C_8), 46.8 (C_5 of 10b), 46.2 (C_4 of 10a). 28.1-22.8 (C_3, C_4 of 10b, C_5 of 10a, C_6, and C_{11}), 14.3 (C_9).

11) NMR (CCl_4) δ 1.70-2.70 (m, 7H, CHCO, CH_2, allylic), 2.13 (s, 3H, CH_3CO), 3.65 (bs, 1H, OH), 3.83 (s, 2H, CH_2O), 5.55 (m, 1H, olefinic).
^{13}C NMR ($CDCl_3$) δ 212.5 (C_8), 137.5 (C_1 of 11a), 136.3 (C_1 of 11b), 122.0 (C_2 of 11b), 120.5 (C_2 of 11a), 66.4 (C_7), 48.0 (C_5 of 11b), 47.3 (C_4 of 11a), 28.1-23.9 (C_3, C_4 of 11b, C_5 of 11a, C_6, and C_9).

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References and Note

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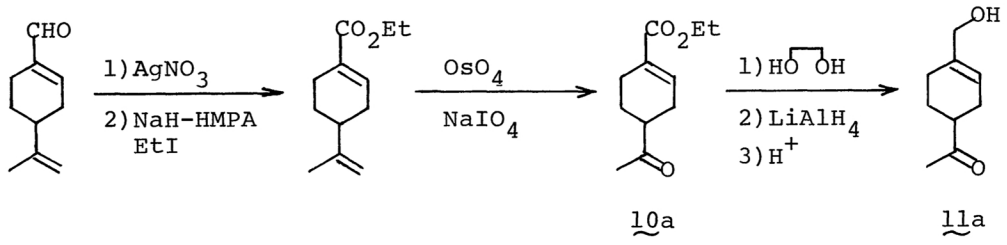

10a 11a

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