

Economical Synthesis of Tetrahydrofurans by Carbonyl-Ene Reaction

Dr. Shilpi Sahana¹, Dr. Sylvia Fernandes²

Assistant Professor, Engineering Chemistry, Dr. D.Y. Patil Institute of Engg., Mgmt. & Research, Akurdi, Pune,
Maharashtra, India ¹

Executive Director, Insulation and Polymers Pvt. Ltd., Dombivili, Mumbai, Maharashtra, India ²

ABSTRACT: Tetrahydrofuran plays a very important role in perfumery and flavor industry. The journal paper deals with the synthesis of tetrahydrofurans from easily available raw material. The synthesis have been achieved through carbonyl-ene reaction promoted by Lewis acid. Along with tetrahydrofurans homoallylic alcohols were also formed during the process and all the products were found to have excellent perfumery odor. Also the process is very economical.

KEYWORDS: tetrahydrofuran, homoallylic alcohol, carbonyl-ene reaction, lewis acid.

I. INTRODUCTION

The synthesis of small heterocyclic compounds, and particularly of tetrahydrofuran derivatives, from common starting materials with a high degree of chemo-, regio- and stereoselectivity has been a target of synthetic chemists for a long time. The tetrahydrofuran and tetrahydropyran derivatives are widely found in many natural products of biological interest. Acetogenins isolated from the Annonaceae family of tropical trees have drawn considerable attention owing to their broad spectrum of biological activities. They are structurally characterized by the presence of one to three tetrahydrofuran rings in the center of along (partly hydroxylated) hydrocarbon chain that ends in a (functionalized) butenolide moiety. Tetrahydrofurans are also found in many perfumes and flavours. The carbonyl-Ene reaction continues to be a powerful C-C bond forming reaction. The carbonyl-Ene reaction promoted by Lewis acid is a powerful tool for the preparation of various homoallylic alcohols ¹⁶⁻¹⁷.

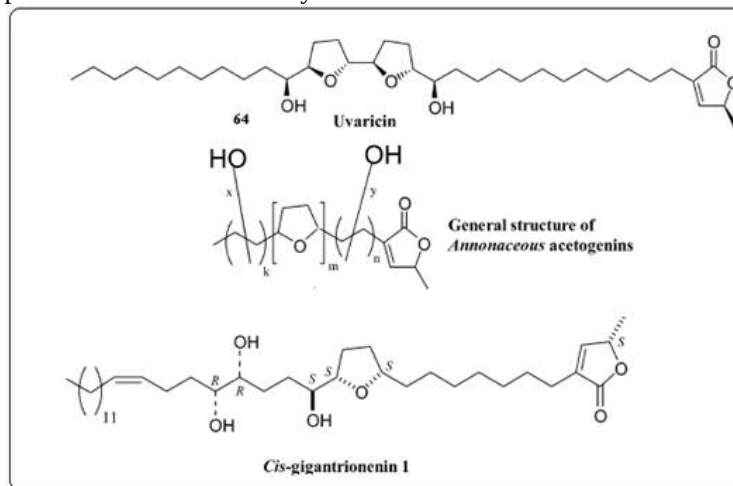


Fig 1 Structure of acetogenin

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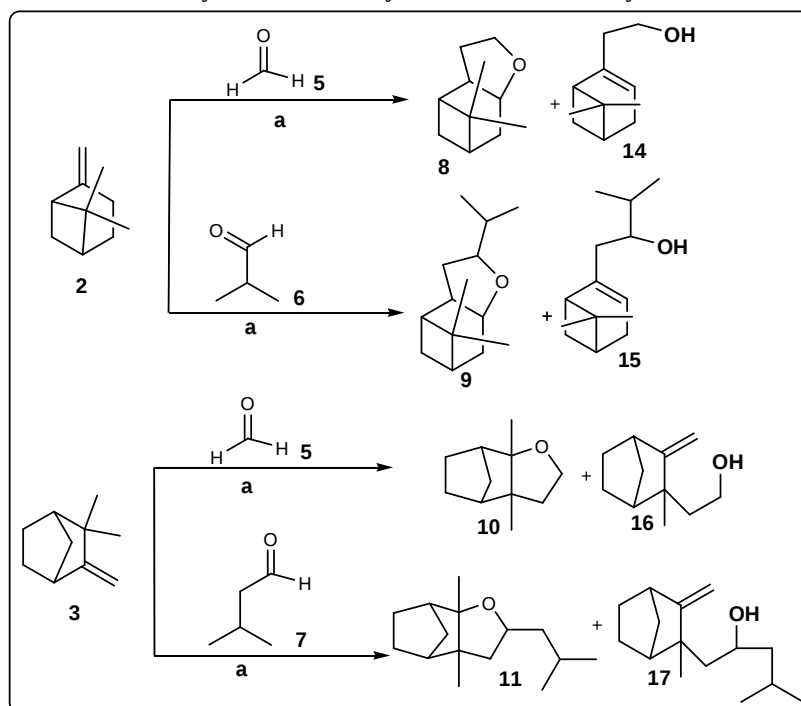
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In the present studies we have synthesized tetrahydrofuran skeleton useful as synthetic intermediate of a perfume, pharmaceutical preparations and agrochemicals. The lewis acid catalysed carbonyl ene reactions of different terpenes (2-4) with various aldehydes (5-7) has been carried out in presence of BF_3 -etherate, molecular sieves and dichloromethane at 0°C , during the reaction we have achieved homoallylic alcohols(14-19) and tetrahydrofurans(8-13).

II. METHOD

To a stirred mixture of terpene 2-4 (3g, 0.022mol), MS-4A molecular sieves (3g) and dichloromethane (20ml) aldehyde 5-7 (0.66g, 0.022mol) was added in drop wise manner and then it is allowed to cool to 0°C . BF_3 -etherate (3.3ml) is added very slowly to the reaction mixture and then the reaction is continued for 5hr at 0°C . It was then quenched with water, and extracted with dichloromethane, washed with brine and dried over anhydrous Na_2SO_4 . The solvent was removed *in vacuo* and the mixture was purified over silica gel column (30 cm x 1.5 cm column, 25 silica gel; 230-400 mesh, 2:8 HOAc-Hexanes) to provide the corresponding tetrahydrofurans(8-13) and homoallylic alcohols(14-19) in yields (Table 4.1).

Scheme 1: Synthesis of tetrahydrofurans and homoallylic alcohols



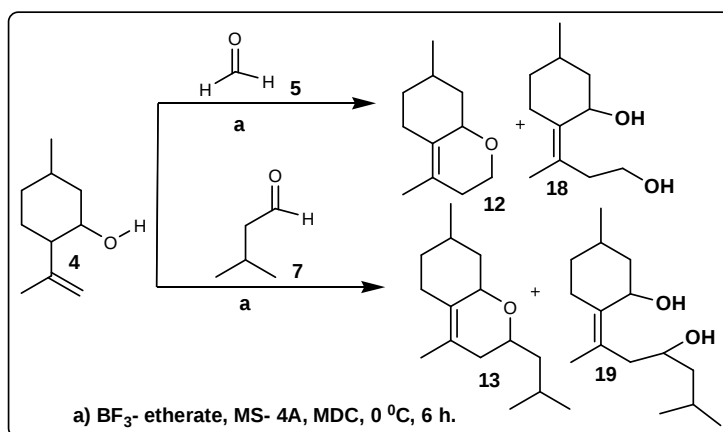
β -pinene (2) and camphene (3) are the reactants used for the experiment which react with various aldehyde such as formaldehyde (5), butyraldehyde (6) and iso-butyraldehyde (7) to form corresponding tetrahydrofuran and homoallylic alcohol.

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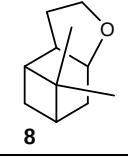
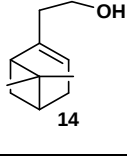
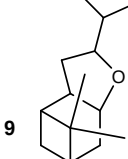
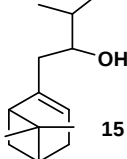
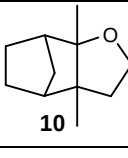
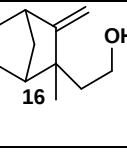


Isopulegol react with aldehydes such as formaldehyde (5) and iso-butryaldehyde (7) to form corresponding tetrahydrofurans and homoallylic alcohol.

III. RESULT AND DISCUSSION

Carbonyl-Ene reaction of terpenens (2-4) with aldehyde (5-7) yielded the tetrahydrofurans(8-13) along with homoallylic alcohols (14-19) in good yields. The homoallylic alcohols underwent in situ cyclization to give tetrahydrofurans. Broad peak at $3650\text{-}3000\text{ cm}^{-1}$ of hydroxy indicated the formation of homoallylic alcohols. The absence of hydroxyl peak indicated that cyclisation has taken place. Furthermore triplet at δ 5.37 and δ 5.5 for olefinic protons for compounds 14 and 15 respectively confirmed the structure. ^1H NMR shows a quartet at δ 3.64 (1H) and δ 3.64(1H) indicating the structure 8 and 9 respectively. The compound 16 and 17 was predicted by a singlet of two proton at δ 5.10 in ^1H NMR corresponded for exo double bond. The compounds 10 and 11 were confirmed by a singlet for methyl group at δ 1.21 and 1.26 respectively. The presence of a triplet at δ 3.8 for 1 proton confirmed the structure of 18 and 19.

Table 1: Products and their yield of the reaction scheme 1

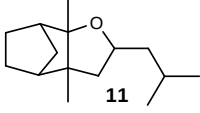
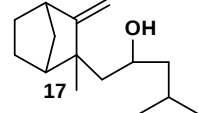
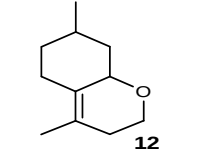
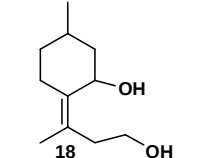
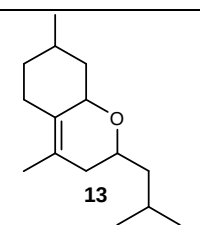
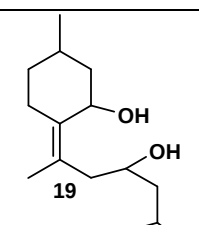
Products		Yields	
A	B	A	B
		52	28
		44	15
		48	12

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		55	30
		40	10
		51	18

The above table explain the different products with yield. Tetrahydrofuran are the major product and the homoallylic alcohol are the minor product.

IV. EXPERIMENTAL SECTION

Tetrahydrofuran of β - pinene(8)

IR (Neat, $\nu_{\max}$): 2956.62, 1455.98, 1367.20, 1260.28, 1215.96, 1105.77, 1058.23, 944.25, 879.96, 837.18, 813.21, 757.51, 665.52 cm^{-1}

^1H NMR (CDCl_3 , 60 MHz): δ 3.75 (t, $J=9\text{Hz}$, 2H), 2.81(q, 1H), 1.95-1.2(m, 9H), 1.15(s, 6H).

GCMS (m/z) 166(M^+), 151, 137, 123, 109, 95, 83, 69, 55, 43.

Tetrahydro-2-isopropylfuran of β - pinene (9)

IR (Neat, $\nu_{\max}$): 2957.16, 1464.65, 1383.67, 1365.75, 1261.14, 1216.07, 1076.17, 760.64, 668.96 cm^{-1}

^1H NMR (CDCl_3 , 60 MHz): δ 3.64(q, 1H), 2.79(q, 1H), 2.69(m, 1H), 1.85-1.19(m, 9H), 1.02(d, $J=5\text{Hz}$, 6H), 1.17(s, 6H).

GCMS (m/z) 208(M^+), 193, 180, 165, 151, 137, 123, 109, 95, 83, 69, 55, 43.

Tetrahydrofuranof camphene(10)

IR (Neat, $\nu_{\max}$): 2924.74, 2867.98, 1456.71, 1381.74, 1284.04, 1145.81, 1124.92, 1085.68, 1031.42, 948.97, 887.87, 837.55, 790.88, 705.10 cm^{-1}

^1H NMR (CDCl_3 , 60 MHz): δ 3.71(t, $J=6\text{Hz}$, 2H), 2.01-1.30(m, 10H), 1.21(s, 3H), 1.17(s, 3H).

GCMS (m/z) 166(M^+), 151, 137, 123, 109, 95, 83, 69, 55, 43

Tetrahydro-2-isobutylfuran of camphene (11)

IR (Neat, $\nu_{\max}$): 2873.67, 1455.59, 1389.78, 1369.84, 1296.00, 1259.04, 1215.68, 1195.39, 1185.01, 1167.57, 1120.52, 1053.00, 1013.86, 987.91, 944.45, 962.06 cm^{-1}

^1H NMR (CDCl_3 , 60 MHz): δ 3.71(m, 1H), 2.01-1.25(m, 13H) 1.26(s, 3H), 1.19(s, 3H), 0.9(d, $J=5\text{Hz}$, 6H).

GCMS (m/z) 222 (M^+), 195, 181, 167, 153, 139, 125, 111, 97, 83, 71, 42

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3,5,6,7,8,8a-hexahydro-4,7-dimethyl-2H-chromene(12)

IR (Neat, $\nu_{\max}$): 2953.78, 2868.94, 1456.64, 1397.79, 1260.10, 1190.00, 1106.69, 1077.71, 981.31, 952.72, 890.01, 874.91, 758.43 cm^{-1}

^1H NMR (CDCl_3 , 60 MHz): δ 3.51(t, J=5Hz, 1H), 2.78(m, 1H), 2.42-1.87(m, 5H), 1.79(s, 3H), 1.75-1.29(m, 7H), 1.19(d, J=4Hz, 3H), 1.09(d, J=4Hz, 6H).

GCMS (m/z) 166(M^+), 151, 137, 123, 109, 95, 83, 69, 55, 43

3,5,6,7,8,8a-hexahydro-2-isobutyl-4,7-dimethyl-2H-chromene(13)

IR (Neat, $\nu_{\max}$): 2873.67, 1455.59, 1389.78, 1369.84, 1296.00, 1259.04, 1215.68, 1195.39, 1185.01, 1167.57, 1120.52, 1053.00, 1013.86, 987.91, 944.45, 962.06 cm^{-1}

^1H NMR (CDCl_3 , 60 MHz): δ 3.71(m, 1H), 2.01-1.25(m, 13H) 1.26(s, 3H), 1.19(s, 3H), 0.9(d, J= 5Hz, 6H).

GCMS (m/z) 222(M^+), 202, 179, 165, 151, 137, 123, 109, 95, 81, 70, 57, 43.

2-(6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)ethanol(14)

IR (Neat, $\nu_{\max}$): 3443.91, 2926.76, 1463.38, 1364.10, 1252.09, 1111.18, 934.14 cm^{-1}

^1H NMR (CDCl_3 , 60 MHz): δ 5.37(t, J=9Hz, 1H), 3.6(t, J=7Hz, 2H), 2.5(t, J=9Hz, 2H), 2.20-1.30(m, 7H), 1.1(s, 6H).

3-methyl-1-(6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)butan-2-ol(15)

IR (Neat, $\nu_{\max}$): 3423.89, 2960.88, 2463.76, 1595.33, 1466.53, 1356.87, 1216.44, 1010.02, 872.72. cm^{-1}

^1H NMR (CDCl_3 , 60 MHz): δ 5.5(t, J=7Hz, 1H), 3.4(q, 1H), 2.5-1.51(m, 10H), 1.11(s, 6H),

0.9 (d, J=5Hz, 6H).

2-(2-methyl-3-methylenebicyclo[2.2.1]heptan-2-yl)ethanol (16)

IR (Neat, $\nu_{\max}$): 3437.69, 2957.82, 1466.97, 1396.82, 1216.28, 1052.09. cm^{-1}

^1H NMR (CDCl_3 , 60 MHz): 5.1(s, 2H), 3.45(t, J=8Hz, 2H), 2.0-1.35(m, 11H), 1.2(s, 3H).

4-methyl-1-(2-methyl-3-methylenebicyclo[2.2.1]heptan-2-yl)pentan-2-ol (17)

IR (Neat, $\nu_{\max}$): 3450.56, 2957.82, 1466.97, 1369.82, 1216.28, 1052.09. cm^{-1}

^1H NMR (CDCl_3 , 60 MHz): 5.1(s, 2H), 3.45(m, 1H), 2.0-1.11(m, 14H), 1.2(s, 3H), 0.95(d, J=5Hz, 6H).

(Z)-2-(4-hydroxybutan-2-ylidene)-5-methylcyclohexanol (18)

IR (Neat, $\nu_{\max}$): 3427.74, 2928.46, 1456.55, 1381.75, 1216.31, 1101.03, 1017.24. cm^{-1}

^1H NMR (CDCl_3 , 60 MHz): δ 3.8(t, J=7Hz, 1H), 3.45(t, J=8Hz, 2H), 2.3-1.75(m, 7H), 1.7(s, 3H), 1.69-1.22(m, 4H), 1.05 (d, J=5Hz, 3H).

(Z)-2-(4-hydroxy-6-methylheptan-2-ylidene)-5-methylcyclohexanol (19)

IR (Neat, $\nu_{\max}$): 3429.85, 2928.32, 1447.20, 1330.29, 1287.32, 1010.03, 1106.44, 1064.51, 943.48. cm^{-1}

^1H NMR (CDCl_3 , 60 MHz): δ 3.8(t, J=8Hz, 1H), 3.45(m, 1H), 2.3-1.72(m, 8H), 1.7(s, 3H), 1.65-1.24(m, 6H), 1.1 (d, J=4Hz, 3H), 0.9 (d, J=6Hz, 6H).

V. CONCLUSION

Tetrahydrofurans are used in perfumery industry, are capable of enlarging and/or improving the palette of odor notes and also found in many natural products. We have successively achieved the synthesis of tetrahydrofurans that have excellent perfumery odor along with homoallylic alcohols through carbonyl-Ene reaction. All the products were synthesized from easily available raw material. The process was proved to be very economical.

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