PART - III

RESULTS AND DISCUSSIONS
SILICON-MEDIATED C-ISOPRENYLATION OF PHENOLS

Natural products bearing an isoprenyl group as such or in the modified form have been exceedingly coming into light during the last two decades\textsuperscript{1,2} and some of them exhibit important biological properties\textsuperscript{3-6}. C-isoprenylation of phenols has been reported to be carried out by two methods. The first method makes use of 3,3-dimethylallyl bromide in basic conditions\textsuperscript{7}. The second method makes use of 2-methyl-but-3-ene-2-ol in presence of BF\textsubscript{3}. In both these methods the reactive species is dimethylallyl cation (X).

\begin{center}
\begin{tikzpicture}
\node (A) {OH};
\node (B) [right of=A] {$+\ \overset{\text{CH}_2\text{Br}}{\text{CH}_2\text{Br}}\ \text{Base}$};
\node (C) [right of=B] {OH};
\node (D) [below of=C] {$\text{BF}_3$};
\node (E) [right of=D] {$\overset{\text{CH}_2\text{C}_2^{-}\overset{\text{CH}_2}{\text{X}}}{\text{X}}$};
\node (F) [below of=E] {$\overset{\text{CH}_2\text{C}_2^{-}\overset{\text{CH}_2}{\text{X}}}{\text{X}}$};

\draw [->] (A) -- (B);
\draw [->] (B) -- (C);
\draw [->] (C) -- (D);
\draw [->] (D) -- (E);
\draw [->] (E) -- (F);
\end{tikzpicture}
\end{center}
It was argued that iodo(trimethyl)silane could add on to isoprene akin to the addition of HBr or HI to furnish compound (Y) which, in presence of excess sodium iodide, would give dimethylallyl iodide as shown in Scheme 1. Dimethylallyl iodide would then act as a potential source of dimethylallyl cation (X) to give the C-prenylated compounds.

Scheme 1

$$\text{H}_2\text{C} = \text{C} - \text{CH} = \text{CH}_2 + \text{Me}_3\text{Si-Cl + NaI (Me}_3\text{Si-I)}$$

$$\text{Me}_3\text{Si-CH}_2 - \text{C} - \text{CH} = \text{CH}_2$$

$$\text{Me}_3\text{Si} - \text{CH}_2 - \text{C} = \text{CH} - \text{CH}_2\text{I (Y)}$$

$$\text{Na}^+ - \text{H}_2\text{C} - \text{C} = \text{CH} - \text{CH}_2\text{I}$$
Reaction of catechol (1) with isoprene in presence of chlorotrimethylsilane and sodium iodide furnished one major and one minor product which were separated (EtOAc:Hexane, 1:4). The major product was identified as the diprenylated catechol (2a) on the basis of NMR spectral analysis. In the NMR spectrum of (2a) a broad singlet 6.60 ppm integrating to two protons was assigned to two aromatic protons, a triplet with \( J = 6.5 \, \text{Hz} \) at 5.20 ppm integrating to two protons was assigned to the olefinic protons of the prenyl groups, a doublet with \( J = 6.5 \, \text{Hz} \) at 3.30 ppm integrating to six protons was assigned to the methylene protons of the two prenyl groups and the four methyls of the two prenyl groups appeared as a broad singlet at 1.80 ppm. The low resolution mass spectrum gave the molecular ion peak at \( m/z \) 246.

Acetylation of the diprenylated product (2a) with acetic anhydride and pyridine furnished the diacetate (2b) in quantitative yield.

The minor component was identified as the cyclized product (3) on the basis of NMR spectrum. In the NMR spectrum the two aromatic protons appeared as a broad singlet at 6.65 ppm, a triplet with \( J = 6 \, \text{Hz} \) at 2.70 ppm.
integrating to four protons and another triplet with \( J=6 \text{ Hz} \) at 1.75 ppm integrating to four protons was assigned to the methylene protons of the two chromane rings and the four methyls appeared as a singlet at 1.40 ppm. The low resolution mass spectrum recorded the molecular ion peak at \( m/z 246 \).

Reaction of resorcinol (4) with isoprene in presence of chlorotrimethylsilane and sodium iodide furnished the monoprenylated compound (5) as the major product and the cyclized product (6) as the minor product. In the NMR spectrum of (5) the presence of an AB system at 6.32 and 6.54 (d, \( J=8 \text{ Hz} \)) and a singlet at 6.30 ppm suggested the introduction of prenyl group at C-4. The vinyl proton appeared as a triplet at 5.23 ppm with \( J=7.5 \text{ Hz} \), the methylene protons of the prenyl group appeared as a doublet with \( J=7.5 \text{ Hz} \) at 3.12 ppm and a broad singlet integrating to six protons at 1.72 ppm was assigned to vinyl methyls.

Formic acid cyclization of compound (5) furnished compound (6) identical in every respect (t.l.c., m.p., NMR, MS) with the minor compound isolated above.

Similarly, the reactions of \( \alpha \)-naphthol (7) and \( \beta \)-naphthol (10) with isoprene in presence of chlorotrimethylsilane and sodium iodide furnished the mono-C-prenylated—
compounds (8) and (11) respectively as the major products and the corresponding cyclized products (9) and (12) as the minor products.

Reaction of resacetophenone (13) with isoprene in presence of chlorotrimethylsilane and sodium iodide furnished (14) as the major product and (15) as the minor product. In the NMR spectrum of the major product (14), the aromatic protons were present as an AB system at 7.30 and 6.30 ppm (doublet, \( J = 8 \) Hz), the vinyl proton appeared as a triplet at 5.32 ppm with \( J = 7 \) Hz, the methylene protons appeared as a doublet at 3.40 ppm with \( J = 7 \) Hz, the vinyl methyls appeared as singlet at 1.80 and 1.70 ppm respectively, and a sharp singlet at 2.40 ppm was assigned to the methyl attached to the keto group.

Formic acid cyclization of (14) furnished compound (15) identical in every respect (t.l.c., m.p., NMR, MS) with the minor compound isolated from the reaction described above.

C-prenylation of phenols has also been achieved with isoprene in presence of toluene-p-sulphonic acid & NaI\(^9\).

To our knowledge this is the first report of direct C-isoprenylation of phenols with isoprene.
\[ \text{(1)} \]
\[ \text{(2)} \quad \text{a, } R = H \]
\[ \text{b, } R = Ac \]
\[ \text{(3)} \]
\[ \text{(4)} \]
\[ \text{(5)} \]
\[ \text{(6)} \]
\[ \text{(7)} \]
\[ \text{(8)} \]
\[ \text{(9)} \]
PART - III

EXPERIMENTAL

General procedure for C-isoprenylation of phenol with CTMS-NaI & isoprene:

A solution of 1 m mol of the substrate in 4 ml of dry acetonitrile was treated with 3 m mol of NaI and 0.5 ml of isoprene followed by 0.5 ml of CTMS. The reaction mixture was stirred at room temperature for 1 to 8 hr monitoring by t.l.c. It was then quenched with 200 ml water and extracted with chloroform. The washed (Na$_2$S$_2$O$_3$ solution and water) and dried extract was evaporated and the residue purified by preparative t.l.c. to get the pure products.

General procedure for cyclization of C-isoprenylated phenols with formic acid:

A solution of 0.5 m mol of the C-isoprenylated phenol in 3 ml of 90% formic acid was heated in a water bath (1 to 2 hr) and the reaction was monitored by t.l.c. After completion of the reaction, it was quenched with cold water and extracted with chloroform. The washed and dried extract was then evaporated under reduced pressure. The residue so obtained was then purified by preparative t.l.c. to obtain the pure product.
**C-isoprenylation of catechol (1):**

The reaction of 100 mg of catechol (1) in 4 ml of dry acetonitrile with CTMS- NaI and isoprene for 4 hr as described in the general procedure furnished after purification by preparative t.l.c. (EtOAc:Hexane, 1:4) 50 mg of (2a) as a gum and 17 mg of (3) also as a gum. Compound (2a) showed NMR peaks at 6.60 s br (two aromatic protons), 5.20 t (J=6.5 Hz, -CH$_2$-CH=CH$_2$, 2H), 3.30 d (J=6.5 Hz, -CH$_2$-CH=CH$_2$, 4H), 1.80 s br (4Me); MS m/z 246 (M$^+$).

Compound (3) showed NMR peaks at 6.65 s br (two aromatic protons), 2.70 t (J=6 Hz, H-4 & H-4'), 1.75 t (J=6 Hz, H-3 & H-3'), 1.40 s (4Me); MS m/z 246 (M$^+$).

**Acetylation of (2a):**

The acetylation of 40 mg of (2a) with Ac$_2$O-Pyridine furnished (2b) in quantitative yield as a gum. It exhibited the following spectral data; IR bands at 3095, 1735 & 1225 cm$^{-1}$; NMR: 6.65 s br (two aromatic protons), 5.20 t (J=6.5 Hz, -CH$_2$-CH=CH$_2$, 2H), 3.25 d (J=6.5 Hz, -CH$_2$-CH=CH$_2$, 4H), 2.20 s (20Ac), 1.70 s br (4Me); MS m/z 330 (M$^+$), 244.
C-isoprenylation of resorcinol (4):

A solution of 100 mg of resorcinol (4) in 4 ml of dry acetonitrile was treated with CTMS-NAI and isoprene as described in the general procedure. The reaction was continued for 3 hr monitoring by t.l.c. After usual work up and purification by preparative t.l.c. (EtOAc:Hexane, 1:3), two products were isolated. The major one was prenylated product (5), yield 40 mg; liquid, lit. \(^8\), \(^10\); liquid b.p. 128\(^\circ\)C; NMR: 6.94 d (J=8 Hz, H-6), 6.32 d (J=8 Hz, H-5), 6.30 s (H-2), 5.74 (OH), 5.23 t (J=7.5 Hz, vinyl proton of prenyl group), 3.12 d (J=7.5 Hz, methylene protons of prenyl group) and 1.72 s br (2Me); MS m/z at 178 (M\(^+\)).

The minor less polar product was 26 mg of (6); m.p. 71\(^\circ\)C. The m.p., NMR and Mass spectral data of (6) were identical with those of its authentic sample \(^8\).

Cyclization of (5) with HCOOH:

Cyclization of 50 mg of (5) with formic acid (90%) as described in the general procedure furnished after purification by preparative t.l.c. (EtOAc:Hexane, 1:5) 40 mg of (6) which was identical with its authentic compound (t.l.c., m.p., NMR and MS).
C-isoprenylation of \( \alpha \)-naphthol (7):

The reaction of 100 mg of \( \alpha \)-naphthol (7) in 4 ml dry acetonitrile with CTMS-NaI and isoprene (for 1.5 hr) as described earlier, after purification by preparative t.l.c. (EtOAc:Hexane, 1:9), furnished two products. The more polar product was (8) as a gum, yield 51 mg; NMR: 7.25 - 7.50 (overlapping signals of H-5, H-6, H-7 & H-8), 6.90 d (J=8 Hz, H-4), 6.50 d (J=8 Hz, H-3), 5.30 t (J=7 Hz, vinyl proton of prenyl group), 3.60 d (J=7 Hz, methylene protons of prenyl groups), 1.75 s br (2Me); MS m/z 212 (M\(^+\)). Anal. calcd. for C\(_{15}\)H\(_{16}\)O: C, 84.87; H, 7.60. Found: C, 84.61; H, 7.36.

The less polar product was (9) as a gum, yield 20 mg; NMR: 7.05 - 7.60 (overlapping signals of H-7, H-8, H-9 & H-10), 6.82 d (J=8 Hz, H-5), 2.84 t (J=6 Hz, H-4), 1.70 t (J=6 Hz, H-3), 1.20 s br (2Me); MS m/z 212 (M\(^+\)).

C-isoprenylation of \( \beta \)-naphthol (10):

The reaction of 100 mg of \( \beta \)-naphthol (10) in 4 ml of dry acetonitrile with CTMS-NaI and isoprene was carried out for 1 hr as described in the general procedure which after usual work up and purification by preparative t.l.c. (EtOAc:Hexane, 1:5) furnished two products. The
The major product was 60 mg of (11), m.p. 114-115°C (CH$_2$Cl$_2$-Bz); NMR: 6.82 - 7.88 (overlapping signals of six aromatic protons), 5.20 t (J=6.5 Hz, vinyl proton of prenyl group), 3.66 d (J=6.5 Hz, 2H, methylene protons of prenyl group), 1.86 s (Me) and 1.61 s (Me); MS m/z 212 (M$^+$); Anal. calcd. for C$_{15}$H$_{16}$O : C, 84.87; H, 7.60; Found: C, 84.48; H, 7.28.

The other less polar product was 20 mg of (12) as a gum; NMR: 7.05 - 7.60 (overlapping signals of H-5, H-6, H-7, H-8 & H-9), 6.80 d (J=8 Hz, H-10), 2.80 t (J=6 Hz, H-4), 1.70 t (J=6 Hz, H-3), 1.20 s br (2Me); MS m/z 212 (M$^+$).

C-isoprenylation of resacetophenone (13):

The reaction of 100 mg of (13) in 4 ml of dry acetonitrile with CTMS-NaI in presence of isoprene was carried out for 18 hr as described earlier which after usual work up and purification by preparative t.l.c. (EtOAc:Hexane, 1:2) furnished two products. The more polar product was 60 mg of prenylated compound (14); m.p. 155°C (MeOH), reported$^{11}$ m.p. 155-156°C; NMR: 13.00 s (OH, hydrogen bonded), 7.30 d (J=8 Hz, H-6), 6.30 d (J=8 Hz, H-5), 5.32 t (J=7 Hz, vinyl proton of prenyl group), 3.40 d (J=7 Hz, methylene protons of prenyl group), 2.40 s (methyl protons of COCH$_3$), 1.80 (Me),
The other less polar product was 20 mg of (15) as a gum which was crystallized from petroleum ether m.p. 70°C, reported m.p. 69-70°C; NMR: 12.85 s (-OH, hydrogen bonded), 7.45 d (J=8 Hz, H-7), 6.25 d (J=8 Hz, H-8), 2.70 t (J=6 Hz, H-4), 2.52 s (methyl protons of COCH$_3$), 1.80 t (J=6 Hz, H-3), 1.46 s (2Me); MS m/z 220 (M$^+$).

**Cyclization of (14) with HCOOH**

Cyclization of 40 mg of (14) with formic acid (90%) as described earlier furnished after purification by preparative t.l.c. 32 mg of (15) which was identical with its authentic sample (t.l.c., m.p., NMR and MS).


   (b) M. Ishinguro, T. Tatsuoka and N. Nakatsuka, ibid, 23, 3859 (1982).


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