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AN EFFICIENT REGIO- AND STEREOSPECIFIC ALKENYLATION OF PHENOLIC ETHERS BY PRENYL AND GERANYL DIISOPROPYL PHOSPHATES[1)]

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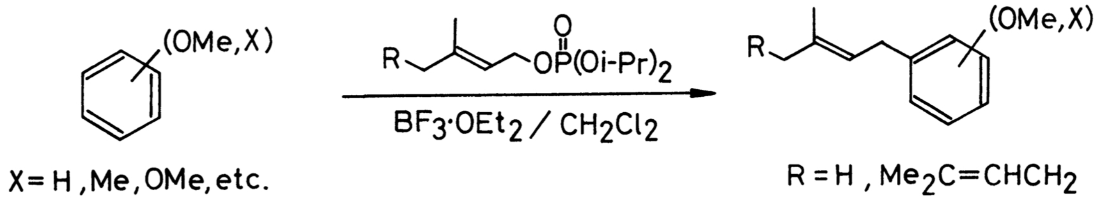
Prenyl and geranyl diisopropyl phosphates readily alkenylate a variety of phenolic ethers regio- and stereospecifically without any appreciable side reactions.

Friedel-Crafts allylation of aromatic compounds using allylic halides or allylic alcohols usually suffers from serious side reactions, e.g., alkylative cyclization, migration of the double bond, and addition of an aromatic compound to the allylic double bond.[2)] Previously we have shown[3)] that allyl diphenyl phosphate successfully allylates aromatic hydrocarbons and phenolic ethers in the presence of boron trifluoride etherate under mild reaction conditions. Although prenylation and geranylation of phenolic compounds are of particular importance from the viewpoint of the syntheses of the natural products such as phenolic isoprenoids and isoprenoid quinones, prenylation of anisole using prenyl diphenyl phosphate has been reported to give p-prenylanisole in only 4.1 % yield.[4)] This poor yield is owing to the thermal instability and the sensitivity to the Lewis acid of prenyl diphenyl phosphate.[5)] We tried to overcome this disadvantage and, after the screening of various allylic phosphates, we found that the use of prenyl and geranyl *diisopropyl* phosphates gave satisfactory results. Here we report the regio- and stereospecific prenylation and geranylation of a variety of phenolic ethers which afford moderate yields of products without formation of any undesired by-products.



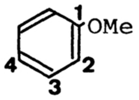
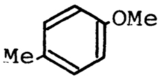
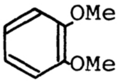
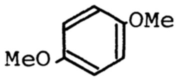
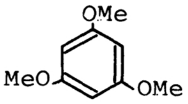
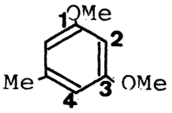
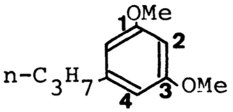
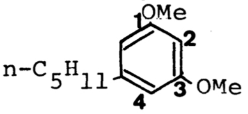
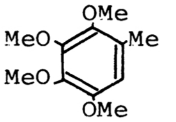
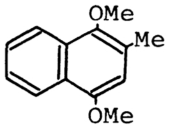
Prenyl and geranyl diisopropyl phosphates were prepared almost quantitatively according to the method for the corresponding diphenyl phosphates,[5)] and could be stored for months without decomposition. The alkenylation was carried out in the presence of boron trifluoride etherate using excess (5 eq to the 1 eq of the phosphate) of aromatic ethers to prevent polyalkenylation. Although the previously reported allylation was conducted at room temperature or below 50°C,[3)] present alkenylation required lower reaction temperature (0°C for prenylation and -23°C for geranylation) to avoid the formation of side products.[6)] The following example is representative. To a mixture of prenyl diisopropyl phosphate (500 mg, 2 mmol) and anisole (1.08 g, 10 mmol) in 6 ml of dichloromethane was added boron trifluoride etherate (0.25 ml, 2 mmol) at 0°C. The mixture was stirred for 4 h at the same temperature and then hydrolyzed. Products were extracted with dichloromethane and washed with saturated aqueous sodium hydrogencarbonate. The solvent and the excess of anisole were distilled off under reduced pressure and the residue was chromatographed on silica gel to afford 2-prenylanisole (58 mg, 16 %) and 4-prenylanisole (204 mg, 58 %). Results for other phenolic ethers are summarized in Table.

The prenylation product of 4-methylanisole (entry 2) was assigned as 2-prenyl-4-methylanisole. The prenylated position was unambiguously confirmed by direct comparison with the authentic sample which was synthesized by the Grignard coupling[7)] of 2-methoxy-5-methylphenylmagnesium bromide with prenyl diethyl phosphate. Geranylation also occurred exclusively at the 2-position of 4-methylanisole. In a similar manner, the reaction products of veratrole (entry 3) were concluded as 4-alkenylveratroles and 3-alkenylated compounds were not found. A series of 1,3-dimethoxy-5-alkylbenzenes (entries 6-8) was readily alkenylated to afford the corresponding 2- and 4-alkenylated products. Thus, dimethylethers of cannabigerovarin[8)] and cannabigerol[9)] could be synthesized in 13 and 15 % yields, respectively, along with their positional isomers. Entries 9 and 10 demonstrate the facile syntheses of the precursors to vitamin K and coenzyme Q which are reported[10)] to be easily oxidized to the biologically active quinones. Aromatic hydrocarbons such as benzene and p-xylene were unsusceptible to alkenylation under the present conditions.

All the reactions were regiospecific, i.e., the substitution occurred at the primary carbon atom (α-position) of the phosphates. Evidence for γ-substitution could not be found. Furthermore, the geranylation products completely retained the original olefin geometry (E-configuration). No traces of Z-isomers were detected by g.l.c. analysis.[11)]

Absence of undesired side reactions, high regio- and stereospecificity, and operational simplicity of these reactions provide a synthetically useful method for the introduction of an allylic side chain to an aromatic nucleus without loss of regio- and stereochemistry.

Table. Reaction of Prenyl and Geranyl Diisopropyl Phosphates with Phenolic Ethers

Entry	Phenolic Ether	Isolated Yield[a] (%)	
		Prenylation	Geranylation
1		16[b] , 58[c]	14[b] , 37[c]
2		68	47
3		68	59
4		62	44
5		61	56
6		9[b] , 57[c]	11[b] , 46[c]
7		11[b] , 61[c]	13[b] , 33[c]
8		20[b] , 56[c]	15[b] , 35[c]
9		51	48
10		52	51

[a] Products were adequately characterized by elemental analyses and spectroscopic data (^{1}H-nmr, ir, and MS).

[b] Yields of 2-alkenylated products.

[c] Yields of 4-alkenylated products.

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References

1) Dedicated to Emeritus Proffessor Takeo SAKAN on his 70th anniversary of birth
2) R.Koneos and B.S.Friedman, "Friedel-Crafts and related reactions" G.A.Olah, ed., Interscience, New York (1964), Vol. II, Part I, pp. 289 - 412.
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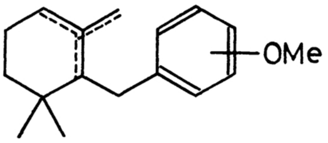
4) Y.Butsugan, K.Saheki, and T.Bito, Nippon Kagaku Kaishi, 1973, 2426.
5) J.A.Miller and H.C.S.Wood, J. Chem. Soc., C, 1968, 1837.
6) When the reaction of anisole and geranyl diisopropyl phosphate, for example, was carried out at room temperature, a mixture of cyclogeranylanisoles formed.



7) S.Araki, T.Sato, and Y.Butsugan, J. Chem. Soc., Chem. Commun., in press.
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9) Y.Gaoni and R.Mechoulam, J. Am. Chem. Soc., 93, 217 (1971).
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11) On the contrary, the reaction with neryl diisopropyl phosphate resulted in complex mixture of products, in which only trace amount of the desired neryl compound could be detected.

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