Cyclopalladation of mixed phosphites as a method of structural modification of natural phenols

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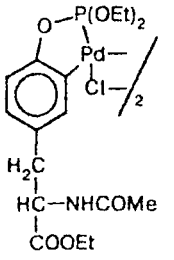
Molecular design requires methods for directed structural modification of the original molecule. Functional groups already present in the molecule are often the starting point for this, and cyclometallation, especially cyclopalladation, occupies an important place among relevant reactions because of the high reactivity of the palladium—carbon bond. However, any cyclometallation requires the presence of a directing atom in the suitable position relative to the H atom to be substituted.

Phenolic hydroxyl, one of the common the functions, has not hitherto found synthetic use for replacing the *ortho*-position of the aromatic ring according to the cyclometallation scheme. In the present report, we proposed a method of activation of the C—H bond in the *ortho*-position relative to the phenolic hydroxyl in the form of mixed phosphite. This approach is based on the cyclopalladation of triphenyl phosphite described earlier,[1] where substitution occurs, of course, at the *ortho*-position of only one aromatic ring of three available. For effective synthetic use of this reaction, phenol should be converted into a mixed phosphite with two inert alkoxy groups.[2] We studied (+)-tyrosine and (+)-estrone as examples of natural phenolic compounds.

N-Acetyl-L-tyrosine ethyl ester ($[\alpha]_D$ +24.0° (EtOH)) was transformed into an *O*-diethoxyphosphino derivative by refluxing with an excess of $Me_2NP(OEt)_2$ without solvent at 100 °C for several hours. Earlier, this phosphite was prepared as an intermediate and transformed immediately into *O*-phosphotyrosine.[3] An L_2PdCl_2-type complex (^{31}P NMR ($CDCl_3$), δ 89.75) was converted into a cyclopalladation product (**1**) (^{31}P NMR ($CDCl_3$), δ 130.3) according to the known procedure[2] by boiling with an excess of $PdCl_2$ in toluene. The signal of one proton in the phenyl fragment of the molecule disappears in the ^1H NMR spectrum of compound **1**.

By analogy, an *O*-diethoxyphosphino derivative was obtained from (+)-estrone ($[\alpha]_D$ +145.4° (CH_2Cl_2)), which was transformed successively into an L_2PdCl_2-type complex (^{31}P NMR ($CDCl_3$), δ 90.1) and a cyclopalladation product (**2**) as a mixture of two regioisomers **2a** and **2b**. This is suggested by the presence of two signals at δ 130.7 and 131.8 (with respect to H_3PO_4) in the $^{31}P\{^1H\}$ NMR spectrum of compound **2**. As with **1**, the signal of one H—C_{aryl} proton disappears in the ^1H NMR spectrum. The major isomer (δ_P 131.8) was isolated in the individual state by crystallization. Presumably, this is the least sterically hindered isomer **2a**. Results of elemental analysis and ^1H and ^{31}P NMR spectroscopy were satisfactory for all new compounds. The study of the substitution of palladium for other groups is in progress.



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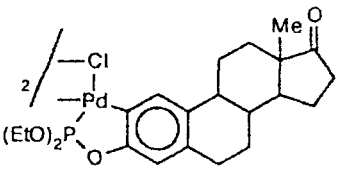

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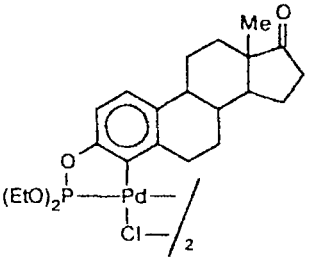

2b

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