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# INTERMOLECULAR AND INTRAMOLECULAR PHENOL PHENYLATION:REGIOSELECTIVE SYNTHESIS OF UNSYMMETRICALLY SUBSTITUTED BIPHENYLS AND 9,10-DIHYDROPHENANTHRENES

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Organic molecules containing as subunits biphenyl groupings or dihydrophenanthrenes skeletons, are very common in nature and many classes of biologically active natural products, have a similar structure. It has been widely recognised that often the formation of the phenyl - phenyl bond in such molecules, constitutes the crucial step in the synthetic pathway, and many studies have been devoted to the solution of this synthetic problem [1,2].

Pschorr type reactions and oxydative phenol coupling [2-9], are the route most commonly involved in such synthesis.

Recently much interest has been raised on this general problem, and important contributions have appeared [1,10,13]. Several natural products have been synthetized by phenol or nonphenol oxydative coupling by means of $VOF_3$ or TTFA. The main problem still open in this approach to substances containing a phenyl-phenyl bond, is the mode of the cyclization, i.e. the possibility of obtaining a coupled product in a regioselective manner: we wish to report that $Ti^{3+}$ ions promoted decomposition of diazonium salts, in presence of phenols, gives phenylated products with the formation mainly of the isomer arising from attack to the *ortho* position with respect to the -OH group. This reaction can be performed both inter- and intramolecularly, constituting a modified Gomberg-Hey [11] and Pschorr [7] reaction.

In the intermolecular series, an anilinium-tetrafluoroborate suspension in water, was treated at 2-3 °C under vigorous stirring , with 1 mole-equivalent of $Ti_2(SO_4)_3$ and then let warm up to room temperature. The ethereal extracts gave a mixture 12,5 : 1 of *ortho : para* hydroxy-biphenyls in a total yield of 35% ++.

The same reaction performed in the Gomberg-Hey conditions, gave comparable total yields,but *ortho : para* ratio of 3 : 1 , as expected.

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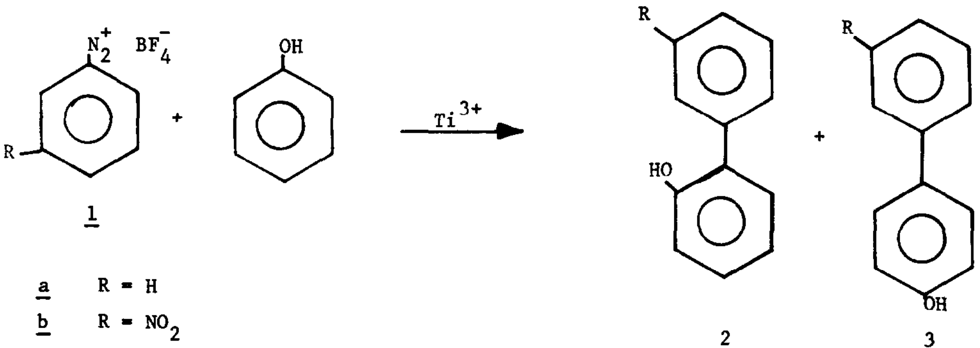
++Determined by GLC

Other substituted anilines behaved in a similar manner.



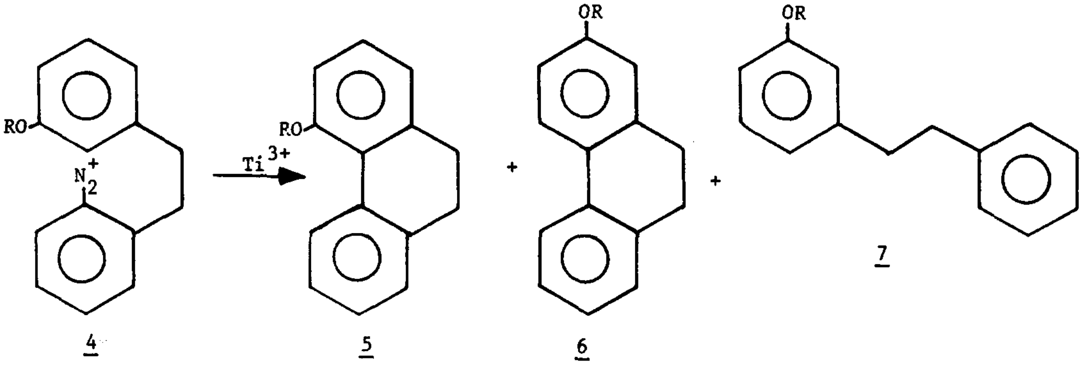
a R = H
b R = $NO_2$
c R = $OCH_3$

TABLE I

| | 2 | : | 3 |
|---|---|---|---|
| a | 12 | : | 1 |
| b | 10 | : | 1 |
| c | 5 | : | 1 |

Reaction products were identified on the basis of their spectroscopic properties and by comparison with samples prepared by unambiguous way.

In the intramolecular series, the reaction was applied on 3'-substituted-1,2-diphenyl-ethane-derived-diazonium salts of type 4, and the results were such as to confirm the trend observed in the intermolecular one.



a R = H
b R = $CH_3$

Table II shows how the *ortho : para* ratio is reversed when going from conditions 1 or 2 to conditions 3 .

Products ratio have been determined by GLC and the products identified by their spectral properties, and by comparison with authentic samples.

TABLE II

| | 1 | 2 | 3 |
|---|---|---|---|
| 5a : 6a ratio | 0.8 : 1 | 0.7 : 1 | 2 : 1 |
| yield of cyclized product | 26 % | 31 % | 31 % |

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1 PSCHORR CONDITIONS 2 PHOTO-PSCHORR CONDITIONS 3 Modified PSCHORR CONDITIONS ($Ti^{3+}$)

In the case of the methyl derivative 4b the product ratio is again in favour of the *ortho* isomer, but in a less pronounced manner ( 5b : 6b ratio = 1.7 : 1 in conditions 3. Yield of cyclized product = 30%).

Cyclization rections were performed by treating a solution of the diazotized compound in a water/methanol or water/dioxan system, with one mole equivalent of an acidic 15% solution of $Ti_2(SO_4)_3$ .The $Ti^{3+}$ solution was added in a 10' time, and the temperature kept at 2-3 °C.The mixture was then directly extracted with ether and the solution examined by gaschromatography.

It is known that diazonium salts decomposition promoted by some metallic ions[12],proceeds via a free-radical mechanism. The *ortho : para* ratio observed in our case in the intermolecular series, are sensibly higher then in ordinary free-radical phenylation of aromatic substrates.On the other hand, reaction of phenyl radicals on phenols, has been little investigated.

The observed results,could be explained,in our opinion, rather then by a "free"-radical mechanism, by a three center concerted reaction, involving -O-group,$-N_2^+$ ,and $Ti^{3+}$.This hypothesis is supported by the observation of the results in the intramolecular series.

We think that the regioselectivity shown in these reactions is of general interest in exploring new methods of synthesis of compounds containing an unsymmetrically substituted 9,10-dihydrophenanthrene moiety.

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