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# An Unusual Non-Radical Phenolic Coupling

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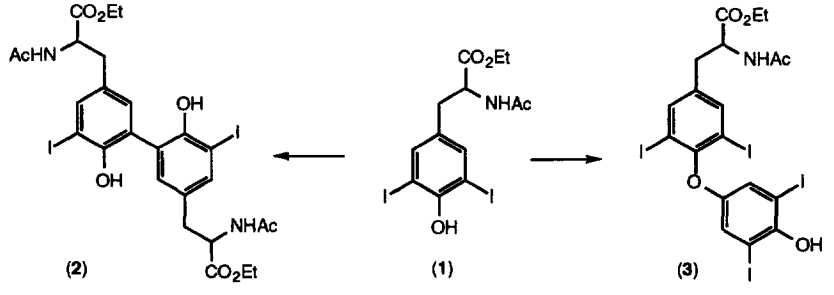
***Abstract:*** *4-Substituted-2,6-diiodophenols undergo non-radical* ortho-ortho *phenolic coupling by an $S_Ni2$ mechanism with liberation of $I_2$ to yield the corresponding biphenyls. In particular, the ethyl ester of* N*-acetyl-3,5-diiodotyrosine gives good yields of the corresponding dityrosine analogue 2 under mild conditions.*


In our studies of the biomimetic synthesis of the hormone, thyroxine,[1] using oxidative phenolic coupling of the ethyl ester of *N*-acetyl-3,5-diiodo-L-tyrosine **1** to yield the ethyl ester of *N*-acetyl-L-thyroxine **3**, we discovered that when the pH dropped < 8, an unusual *ortho-ortho* C-C coupling of diiodotyrosines with loss of two iodines to yield the corresponding dityrosine **2** took place. Oxidative *ortho-ortho* C-C coupling is well known in the extensive studies of phenolic coupling but is unknown when halogens are present.[2] At higher pH (> 9) and in the presence of oxygen the thyroxine **3** was exclusively formed (EtOH/water, borate buffer, oxygen). In a nitrogen atmosphere the dityrosine **2** is formed at lower pH and neither the dityrosine **2** nor the thyroxine **3** are formed at higher pH. The phenolic coupling to form thyroxine is known to proceed *via* the phenoxyl radical and requires oxygen as an oxidant.[1] In this paper we report our studies of the mechanism and generality of the unusual non-radical phenolic coupling.

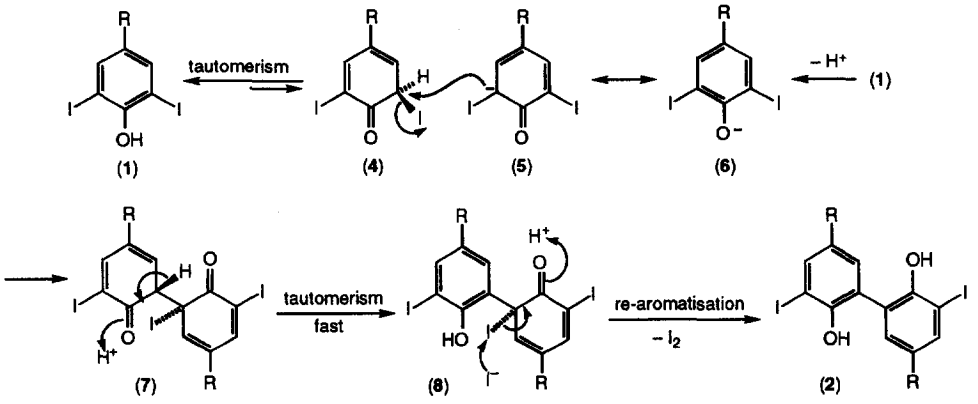



The 3,5-diiodo-L-tyrosine **1** was used to study the mechanism of the reaction. The reaction conditions for the thyroxine synthesis (EtOH/water, borate buffer, oxygen) proved unreliable and after extensive study, a two phase $CH_2Cl_2$ and borate buffer reaction mixture at room temperature was found to give the best yields [% yield of **2**: 1 day (50%), 3 days (75%), 4 days (66-80%)].[3] At 5 °C, the yields were minimal. The use of THF, DMSO, DMF, and $Et_2O$ in place of $CH_2Cl_2$ as solvent gave no yield of **2**, with unaltered **1** recovered quantitatively. $CH_2Cl_2$ alone as solvent was less satisfactory [**2** (16%), 4 days, $O_2$ or $N_2$]. The reactions were clean and only coupled dimers and starting materials were isolated in quantitative mass balance.

The control of pH proved crucial and either borate or phosphate buffers proved satisfactory [% yield of **2** after 1 day: borate buffer, pH 6.4 (50%); phosphate buffer (50%)]. The $pK_a$ of **1** is 6.35 and within the pH range 3.0 - 8.0 the yield was generally similar [% yield of **2**: 1 day, pH 4.1 (50%); 2 days, pH 4.3 (60%), 4.6 (60%), 5.9 (72%); 4 days (6.3 and 7.1 (66%). The yields were higher when the reaction was carried out in a

pressure reactor at 5 bar, but at high pH no reaction took place (**2**, 40%, 6.5 h, pH 6.5; **2**, 0%, 6.5 h, pH 8.9). All the reactions turned pink and then dark purple as the iodine was liberated. In a standard reaction for 4 days using sodium thiosulfate, a 16% yield of **2** was obtained and iodine titrated for 12.4%.

The yield of the coupling reaction product **2** was unaffected when carried out under an atmosphere of oxygen or nitrogen [1 day: in $O_2$ (**2**, 33%) and in $N_2$ (**2**, 33%); 3 days: in $O_2$ (**2**, 75%) and in $N_2$ (**2**, 75%)] which clearly indicates that oxidation *via* phenoxyl radicals is not taking place. This conclusion is supported by the knowledge that oxidative coupling of **1** proceeds *via* phenoxyl radicals and gives exclusively oxygen-*para* coupling to yield **3** and requires oxygen as an oxidant. The radical coupling of **1** to **3** also yields some polymeric material which is common in phenoxyl coupling reactions, but is absent in the conversion of **1** to **2**. Further studies were carried out to determine the effect of a phase transfer catalyst (PTC) (benzyltrimethylammonium hydroxide), radical inhibitors (TEMPO, 1 equiv.), and light catalysis (exclusion of light). The reactions were run for 1, 3, and 4 days respectively: standard reaction[3] [yield of **2** (50, 62, 66% resp.)], with PTC [yield of **2** (50, 66, 66% resp.)], exclusion of light [yield of **2** (33, 40, 50% resp.)], and with TEMPO added [yield of **2** (75, 63, 62% resp.)]. The use of a phase transfer catalyst did not affect the yield and the difference in yields for the addition of TEMPO were not significant. The exclusion of light gave slightly reduced yields but within the range of yield variation for the reactions.

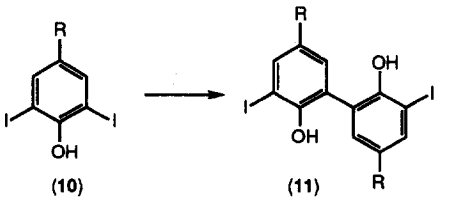



**Scheme 1.** Putative $S_N2$ mechanism for the phenolic coupling. R = $CH_2CH(NAc)CO_2Et$

We consider that our results indicate a non-radical mechanism we propose the $S_N2$ mechanism shown in Scheme 1. The central assumption is that a small amount of the α-iodoketo tautomer **4** is formed which undergoes $S_N2$ with the ambident phenolate anion **5** *via* its *C*-centre to yield the intermediate **7**. The α-iodoketo tautomer **4** is an intermediate in the di-iodination of the ethyl ester of *N*-acetyltyrosine. The diketo intermediate **7** will undergo rapid tautomerism to the more stable phenol form **8**, which in turn will lose iodide with re-aromatisation as the driving force. The iodine thus generated is clearly observed in all the reactions. Use of molecular modelling (Chem 3D/MM2) for **4** indicates that there is low steric hindrance to approach once the C-atom to which the α-iodo group is attached becomes $sp^3$ hybridised and the α-iodo group moves out of the plane. An equivalent $S_N2$ mechanism has been proposed for the 1,1'-phenolic coupling, with loss of bromide, between 1-bromo-2-naphthol and the anion of 2-naphthol.[4] The C-1 to oxygen phenolic coupling between 1-bromo-2-naphthol and the anion of 2-naphthol[4] and the anion 1-bromo-2-naphthol[5] have also been reported. There are no previous reports of the non-radical coupling of 4-substituted-2,6-diiodophenols.

The ethyl ester of 3,5-dibromo-*N*-acetyltyrosine and the ethyl ester of 3-iodo-*N*-acetyltyrosine **9** do not undergo coupling under the same conditions. A variety of conditions and pH (at their $pK_a$'s and lower pH's) were tried without success. A mixture of the 3-iodo-*N*-acetyltyrosine **9** and **1** yield the dityrosine **2** but **9** is recovered in quantitative yield indicating that it has not participated in the reaction. These results suggest that

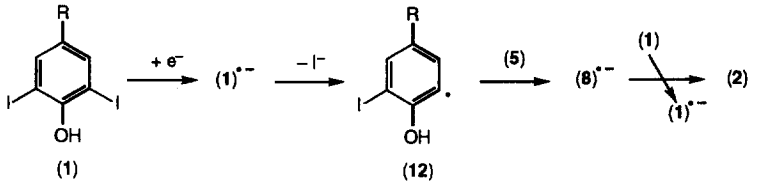
only the 3,5-diiodotyrosine generates the α-halogeno keto-tautomer required for coupling. A range of other 4-substituted 3,5-diiodo-phenols also undergo the coupling reaction. The reasons for the unique behaviour of diiodo-phenols and the requirement for the two phase reaction mixture are not clear.




(10), (11)
a, R = $CH_2CO_2Et$
b, R = $CH_2CH_2CO_2Et$
c, R = $CH_2CH_2NHAc$
d, R = $CH_2C(Me)(NHAc)CO_2Et$
e, R = Me
f, R = Pr
g, R = $CO_2Et$
h, R = CHO
i, R = $CH{=}C(NHAc)CO_2Et$

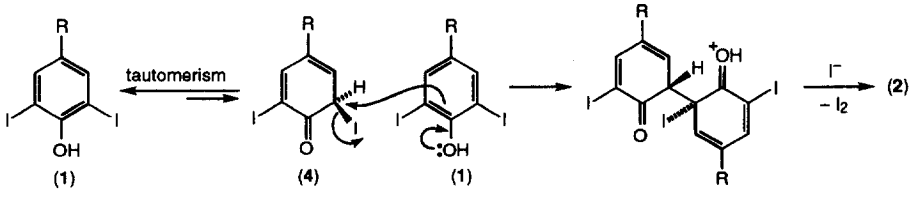
A range 4-substituted 3,5-diiodo-phenols, **10a** - **10i**, were reacted under the same conditions but yields were not optimised.[3] The diiodophenols **10a** - **10d** gave the corresponding biphenyls and the yields were as follows: **10a**, 4 days (**11a**, 22%), **10b**, 3 days (**11b**, 33%), and **10c**, 4 days (**11c**, 62%). The α-methyl diiodotyrosine **10d**, when reacted in EtOH/aqueous borate buffer for 2 days, gave the dimer **11d** (45%). The diiodophenols, **10e** and **10f** did not react under the standard conditions,[3] but under alternative conditions [24 h, toluene, 80 °C, *t*-BuOK (0.5 equiv.)], **10e** gave **11e** (40, 47%), **10f** gave **11f** 16%, and **1** gave **2** (16%). Diiodophenols, **10g** - **10i** did not couple under any of the conditions attempted, which suggests that conjugation of the 4-substituent discourages tautomerism onto the *ortho*-carbon atom and hence prevents coupling.

Aromatic $S_{RN}1$ reactions[6] are known for the reaction between naphthoxides and iodoarenes[7] and could possibly explain the coupling reactions (Scheme 2). Electron addition by single electron transfer followed by loss of iodide to yield the intermediate σ–radical intermediate **12** would help overcome the steric problems and guide coupling *via* the ortho position for the iodoarene but the phenolate anion is more likely to react *via* the *para*-position. However, the $S_{RN}1$ substitution is a chain reaction and easily inhibited. We observed no noticeable inhibition with oxygen, TEMPO or absence of light, all of which are good indicators for the chain $S_{RN}1$ mechanism, and therefore rule out the $S_{RN}1$ mechanism.




**Scheme 2.** Putative $S_{RN}1$ mechanism for the phenolic coupling. R = $CH_2CH(NAc)CO_2Et$

Neutral solutions of the diiodotyrosine **1** in EtOAc:$H_2O$ (10:1) at room temperature released iodine and gave the dityrosine **2** (5 days, 20%; 10 days, 33%). We suggest that the mechanism (Scheme 3) is similar to that shown in Scheme 1 and that the diiodophenol **1** is able to react with its tautomer **4** and does not need to be ionised but that the reaction is much slower.




**Scheme 3.** Putative $S_N2$ mechanism for the phenolic coupling in EtOAc. R = $CH_2CH(NAc)CO_2Et$

In the EtOAc reaction, there was no significant difference in yields under an atmosphere of oxygen or nitrogen and in light or exclusion of light. However, no reaction was observed even after 10 days in dry EtOAc or when catalytic acid (HOAc) or base ($Et_3N$) were added. Other diiodophenols also gave dimers, e.g. in EtOAc:$H_2O$ (10:1) solution for 10 days, **10a** yielded **11a** (13%), **10b** yielded **11b** (4%), and **10c** yielded **11c** (40%), but the diiodophenols, **10e** and **10f**, and the ethyl esters of 3,5-dibromo-*N*-acetyltyrosine and 3-iodo-*N*-acetyltyrosine did not give any reaction.

Interestingly, the *ortho-ortho* C-C couplings of diioodotyrosines to the corresponding dityrosines using oxidation by electrolysis or thallium (III) trinitrate, followed by Zn/AcOH reduction, have been reported.[8] The authors propose that the coupling proceeds *via* intermediate phenoxyl radicals. We suggest that this reported coupling[8] could also be by a $S_N2$ mechanism. The phenolate anion and the phenoxyl radical of the 3,5-diiodotyrosine moiety are both planar due to delocalisation of electrons. Use of molecular modelling (Chem 3D/MM2) indicates that the phenolate anion, or phenoxyl radical, of the 3,5-diiodotyrosine moiety cannot sterically approach the second phenoxyl radical due to the large steric bulk of the *ortho*-iodine atoms. The corresponding 3,5-dibromotyrosines[8,9] yield *O-ortho* coupling which suggests that a phenoxyl mediated coupling may explain the mechanism for the dibromo analogue. Molecular modelling indicates that the *O*-centre of the phenolate anion of the 3,5-dibromotyrosine moiety, but not the corresponding *O*-centre of the 3,5-diiodotyrosine, is able sterically approach the *ortho*-carbon of the corresponding phenoxyl radical. This lower steric hindrance explains the *O-ortho* coupling for the dibromo series for either phenoxyl mediated or $S_N2$ coupling. The coupling of tyrosine to yield dityrosine has been achieved using peroxidase and $H_2O_2$.[10]

In summary, we have shown an unusual non-radical phenolic coupling which provides a facile protocol for *ortho-ortho* coupling of 4-substituted-2,6-diiodophenols for the synthesis of dityrosine natural products. A high yielding synthetic method uses rhodium (III) catalysed coupling of 4-substituted phenols.[11]

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