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Novel Catalyzed Coupling Reaction OfAromatic Heterocyclic Estradiol Derivatives

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Abstract: *During the last two decades, there have been considerable interest in the palladium mediated C-C coupling reaction. Last year, the noble Prize in chemistry was awarded to three scientist for their extensive work in palladium chemistry .Palladium catalyzed annulations reaction of alkynes are of eminence for the synthesis of variety of hetero and carbocyclic ring system. Recently palladium alkyne annulations reaction offered useful and convenient route to indoles, benzofuran, benzopyrans, indenones and isocoumarins.Estrogen analogue containing such moieties could be of use as anticancer and antiviral agent . An attempt has been made to synthesize such steroidal molecules .*

Keywords*: Palladium catalyst,Steroids,Homogeneous, Hetero,Moieties,Synthesize*

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I. Introduction

There have been considerable interest in the palladium mediated C-C coupling reaction. Last year, the noble Prize in chemistry was awarded to three scientist[1] for their extensive work in palladium chemistry . The transition metal mediated cycloaddition of alkynes are of great current interest[2], While palladium is among the most widely studied metal for such processes[3a,b]. It accommodate a number of different functional group[4].Palladium catalyzed annulations reaction of alkynes are of eminence for the synthesis of variety of hetero and carbocyclic ring system.[2,5]. Recently palladium alkyne annulations reaction offered useful and convenient route to indoles[6], benzofuran[7], benzopyrans[8], indenones[9] and isocoumarins. Estrogen analogue containing such moieties could be of use as anticancer and antiviral agent . An attempt has been made to synthesize such steroidal molecules.

New heterocyclic aromatic derivatives using palladium as catalyst is synthesized and characterized .Palladium catalyzed annulations reaction of alkynes are of eminence for the synthesis of variety of hetero and carbocyclic ring system. The synthesis was achieved by selecting steroidal compounds bearing amino groups .Estrogen analogue containing such moieties could be of use as anticancer and antiviral agent.

Reaction of 17α-ethynyl estradiol (LVI) with orthoiodo phenol , orthoiodo aniline , orthoiodobenzaldehyde and with orthoiodo methyl ester : It is dissolved in DMF , added triethyl amine, $P(PPh_3)PdCl_2$ and CuI in o –iodophenol and K_2CO_3 (anhydrous) as a base, LiCl ,Pd($OAc)_2$ were added in case of o-iodo aniline and NaOAc as a base and n-tetrabutyl ammonium chloride, $Pd(OAc)_2$ were added in o-iodobenzaldehyde and in case of o-iodo methyl ester , triphenyl phosphine and excess of sodium carbonate as a base , Pd($OAc)_2$ as a catalyst , analytically pure samples were obtained using reverse phase column chromatography .

Purity of the main compound was checked by thin layer chromatography(TLC). TLC was carried out on pre coated silica plates containing fluorescent indicator (UV-254 nm).Crude reaction mixture were purified by high performance liquid chromatography (HPLC) using methanol and water (80:20). ^{1}H- NMR spectra were recorded on a Brucker Ac 300(300mhz) in $CDCl_3$ or DMF $–d_7$ solution. High and low resolution mass spectra (HRMS,MS) were determined with a VG Micro massmodel ZAB-IF apparatus at 70ev. ionization voltage.

II. Experimental

2.1 Synthesis of 17 α- Benzofuran Estradiol (LIX)

Compound eluted at Rt =11.27 min.The mass spectrum gave a molecular ion peak at m/z 388,corresponds to the substitution of iodine leads to the benzofuran ring and this was confirmed by HRMS 388.2032 (exp.). ^{1}H-NMR gave a doublets for C4'-H at δ7.5 J= 8.1 Hz,C5'-H at δ7.1, J=7.6 Hz ,C6'-H at δ7.2,J= 8.0 Hz for C7'-H at δ7.4, J=7.8 Hz and singlet at δ6.5 for C3'.This confirm the structure of above compound as (LIX) .

2.2 Synthesis of 17 α- Benzopyrrole Estradiol (LX)

Compound eluted at Rt=19.5 min and the MS-spectrum shows a peak at m/z 387which confirms the presence of benzopyrrole ring moiety attached at 17α-position of estradiol and this was supported by HRMS 387.296(exp.) gives the composition of $C_{26}H_{29}NO_2$ in the mass spectrum.^{1}H-NMR gave a singlet at δ 6.0 for C3'-proton of benzopyrrolering. The structure has been confirmed on the mass spectrum required two endocyclic vinylic proton, one in benzopyrole ring another in five membered ring of estrone skeleton, but since ^{1}H-NMR, we are getting one singlet for endocyclic vinylicproton , which is already decided for endocyclicbenzopyrrole ring proton.

It seems that during electron impact, in the process of mass spectral analysis tertiary hydroxyl group of estradiol is eliminated as water molecule leading to structure (LX) and doublets for C4'-H at δ7.6 J=8.0Hz,C5'-H at δ7.0,J=7.5 Hz ,C6'-H at δ7.2,J= 8.4Hz for C7'-H at δ7.4,J=8.0 Hz and broad singlet for N-H proton confirming the benzopyrrole ring in above structure.

2.3 Synthesis of 17 α- Indenone Estradiol (LXI)

Compound eluted at Rt =20.15 min and the MS-spectrum shows a peak at m/z 400 which corresponds to cyclized ring leading to compound (LXI) and this was further supported by HRMS 400.204 (exp.).^{1}H-NMR gave a doublets for C4'-H at δ7.7 J= 8.0 Hz,C5'-H at δ7.0, J=7.8 Hz, C6'-H at δ7.2, J= 8.2 Hz and for C7'-H at δ7.4, J=7.5 Hz and a singlet at δ6.3 for C3'-H. These above data correspond to the structure (LXI)

2.4 Synthesis of 17 α- Isocoumarin Estradiol (LXII)

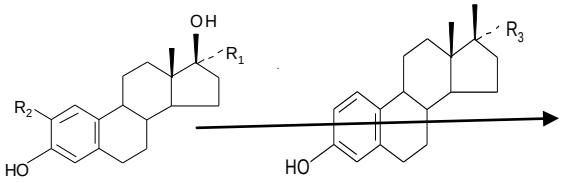
Compound eluted at Rt =11.90 min. and the mass spectrum shows peak at m/z 416, which corresponds to the cyclized ring structure leading to compound (LXII).^{1}H-NMRspectrum shows doublets for C8'-H at δ7.8, J=7.2 Hz,C7'-H at δ7.2, J= 7.4 Hz,C6'-H at δ7.4, J=8.2 Hz and for C5'-H at δ7.5, J=7.9 Hz and singlet for C3'-proton at δ6.6 confirming the above structure as (LXII).

III. Result and Discussion

The main compounds were obtained by the major reaction with 17α-ethynyl estradiol (LVI) with orthoiodo phenol , orthoiodo aniline, orthoiodobenzaldehyde and with orthoiodo methyl ester :

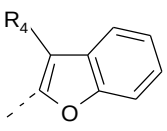
It is dissolved in DMF, added triethyl amine, $P(PPh_3)PdCl_2$ and CuI in O-iodophenol and K_2CO_3 (anhydrous) as a base, LiCl,$Pd(OAc)_2$ were added in case of O-iodo aniline and NaOAc as a base and n-tetrabutyl ammonium chloride,$Pd(OAc)_2$ were added in O-iodobenzaldehyde and in case of O-iodo methyl ester, triphenyl phosphine and excess of sodium carbonate as a base, $Pd(OAc)_2$ as a catalyst, heated at 90-100 C for 24-30 hour under nitrogen atmosphere. After usual work up, analytically pure samples were obtained using reverse phase column chromatography (HPLC methanol :water) (85:15) in case of o-iodo aniline and o-iodo methyl ester and ratio of (Methanol : water) (80:20) in case of O-iodo phenol and O-iodobenzaldehydeand finally gave the four products (LIX),(LX), (LXI) and (LXII) respectively.

Synthesis route is depicted in scheme -I :

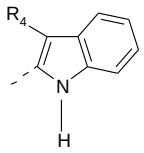


R1R2R3

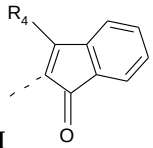
(LVI)-C≡ C-H H



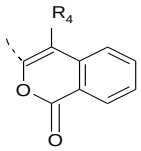
(LIX)R4=H



(LX)R4=H



(LXI)R4=H



(LXII) R4=H

Scheme -I

IV. Conclusion

This article summarized the novel synthesisand characterization of new heterocyclic aromatic derivatives using palladium as catalyst. Palladium catalyzed annulations reaction of alkynes are of eminence for the synthesis of variety of hetero and carbocyclic ring system. The synthesis wasachieved by selecting steroidal compounds bearing amino groups.Estrogen analogue containing such moieties could be of use as anticancer and antiviral agent.

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