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Palladium Heteroannulation Process for Synthesis of Substituted Pyrrolo[2,3-*b*]Pyridin-3-ones

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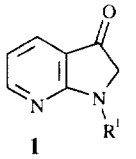
Abstract: Substituted-3*H*-pyrrolo[2,3-*b*]pyridin-3-ones **7b-d** were prepared from 2-amino-3-iodo-pyridine derivatives **3b-d** by palladium carboannulation process with allenic compounds and then oxidative cleavage of the exocyclic carbon-carbon double bond.

Substituted-3*H*-pyrrolo[2,3-*b*]pyridin-3-ones or 7-azaindolinones **1** are versatile compounds for the preparation of azaindolic derivatives. As previously reported,[1] standard preparations of indolinones failed to yield 7-azaindolinones and we investigate new strategies to synthetise these compounds. We have already proposed a Baeyer-Villiger oxidation of 3-carboxaldehyde-1*H*-pyrrolo[2,3-*b*]pyridines[1] but the high cost of 7-azaindole and the limited possibilities of substitution (particularly in 5-position) lead us to investigate a new approach by creating the 7-azaindolic framework, by palladium heteroannulation, which can also be used in the synthesis of aza-analogues of Duocarmycins **2** (potent antitumor antibiotics).



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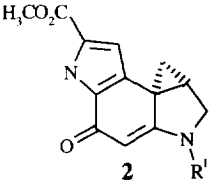
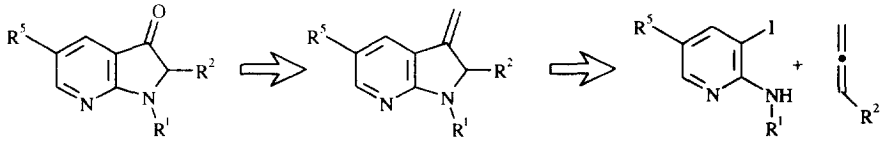


2

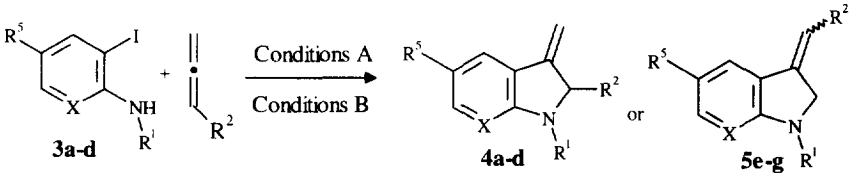
5-Substituted-3-iodo-2-aminopyridines are easily available by metalation reactions[2] and can be used for palladium-catalysed cross coupling reactions to provide 3-methylene-1,5-substituted-pyrrolo[2,3-*b*]pyridines as shown in the retrosynthetic scheme.



Larock has reported on the annulation process between iodo-aryl compounds and 1,2 dienes,[3] 1,3 dienes,[4] 1,4 dienes[5] and alkynes;[6] carbopalladation of allenes is well-documented;[3,7] the allenic compounds used were either alkyl substituted[3] or possessed an heteroatom.[13b,c] We report in this letter the

synthesis of 3-methylene-pyrrolo[2,3-*b*]pyridine derivatives using 1-substituted-1,2-propadienes and substituted 3-iodo-2-aminopyridines. The cyclisation, performed with *N*-tosyl-2-iodoaniline **3a** and 1-methoxypropadiene[8] in the presence of $Pd(OCOCH_3)_2$ (conditions A) afforded exclusively the 1,2-dihydro-2-methoxy-3-methylene-1-tosyl indole **4a** with the same regioselectivity as reported for Larock's 1,2-undecadiene (scheme 1).[3a]

Switching for the azaanalogues, we obtained in the same way compounds **4b-d** using $Pd(PPh_3)_2Cl_2$ and CH_3CN as solvent (conditions B); the use of $Pd(OCOCH_3)_2$ / PPh_3 and DMF as solvent (Conditions A) was unproductive (mainly degradation). Di *t*-butyl-1,2-propadienylphosphonate[9] (R^2 = $PO[OC(CH_3)_3]_2$) gave the other regioisomers **5e,f** without substituent in 2-position (scheme 1).

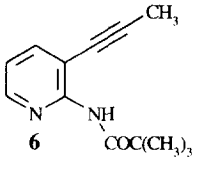


3	R^1	R^2	R^5	X	Conditions	Reaction time	4,5	Yield of 4 (%)	Yield of 5 (%) (*Z* / *E*)
a	$SO_2C_6H_4CH_3$	OCH_3	H	CH	A	5 h	**a**	75	-
a	$SO_2C_6H_4CH_3$	OCH_3	H	CH	B	5.5 h	**a**	60	-
b	$SO_2C_6H_5$	OCH_3	H	N	B	3 h	**b**	65	-
c	$COC(CH_3)_3$	OCH_3	H	N	B	3 h	**c**	80	-
d	$COC(CH_3)_3$	OCH_3	Br	N	B	3 h	**d**	75	-
a	$SO_2C_6H_4CH_3$	$PO[OC(CH_3)_3]_2$	H	CH	B	14 h	**e**	-	50 (30 / 70)[b]
c	$COC(CH_3)_3$	$PO[OC(CH_3)_3]_2$	H	N	B	12 h	**f**	-	80 (30 / 70)[a]
d	$COC(CH_3)_3$	$PO[OC(CH_3)_3]_2$	Br	N	B	12 h	**g**	-	80 (30 / 70)[b]

Conditions A: 1 mmol of **3a**,[11] 2 mmol of allene, 0,05 mmol of $Pd(OCOCH_3)_2$, 0.05 mmol of PPh_3, 1 mmol of $C_6H_5CH_2(CH_3CH_2)_3N^+Cl^-$, 3 mmol of Na_2CO_3 in 4 ml of DMF are heated at 90°C during the time indicated. *Conditions B*: 1 mmol of **3a-d**,[2] 2 mmol of allene, 0.10 mmol of $Pd(PPh_3)_2Cl_2$, 1 mmol of $C_6H_5CH_2(CH_3CH_2)_3N^+Cl^-$, 3 mmol of Na_2CO_3 in 4 ml of CH_3CN are heated at 90°C during the time indicated. [a] isolated stereomers, [b] ^{1}H-NMR ratio.

Scheme 1

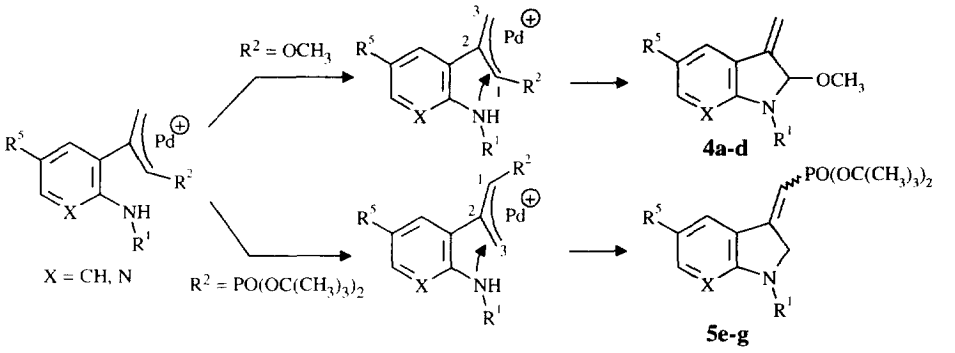
Attempts with stannylallene (R^2 = $Sn[(CH_2)_3CH_3]_3$) and **3c** afforded 2,2-dimethyl-N-[3-(propyn-1-yl)pyridin-2-yl] propanamide **6** which results from the classic cross-coupling process involving stannyl compounds.[10] Degradation was observed with other allenic derivatives (R^2 = $COOC_2H_5$, $C{\equiv}CCH_2OH$).



6

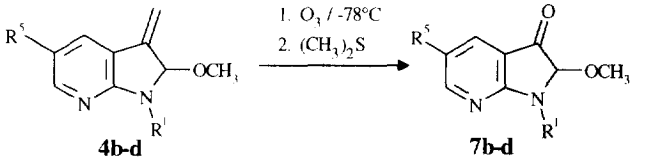
Two stereomers *Z/E* were obtained during the synthesis of **5e-g** and isomerisation of the minor stereomer *Z* to the *E*-isomer was observed in two days at room temperature.

Two different pathways can explain the outcome of the cyclisation. The first is the formation of a pyridinylpalladium compound followed by the π-allylic complexation of allenic derivative as reported for aryl derivatives.[12] Since the presence of polar substituents on terminal carbons of the π-allylic system influences the regiochemistry of the reactions,[13a,b,c] nucleophilic attack of nitrogen atom on the most electron-deficient carbon atom of the π-allyl system affords either **4** or **5**. With methoxyallene, the methoxy group stabilises the most electrophilic carbon, C-1 in this case.[13b,c] With allenic phosphonate, however the C-3 atom is the most positive, due to the electronic effect of the phosphonate group (scheme 2). Helquist has reported the same regioselectivity during palladium-catalyzed amination of 1,3-pentadienyl phosphonate ester.[13d]



Scheme 2

Different methods were performed to cleave the carbon-carbon double bond of compounds **4a-d** into keto compounds **7a-d**; osmium tetroxide/sodium periodate,[14] heterogeneous permanganate oxidation[15] and ozonolysis[16] ; the best method of oxidation was the ozonolysis reaction (scheme 3).



4	R^1	R^5	Reaction time	7	Yield of 7 (%)
b	$SO_2C_6H_5$	H	0.15 h	**b**	25
c	$COC(CH_3)_3$	H	0.3 h	**c**	54
d	$COC(CH_3)_3$	Br	0.3 h	**d**	50

Ozonolysis: bubbling ozone, 0.40 mmol of **4b,c,d** in 3 ml of CH_2Cl_2 at -78°C then addition of $(CH_3)_2S$.

Scheme 3

Some traces of 2-aminonicotinic are found during ozonolysis of compound **4c**; the oxidation of indolic compound **4a** with $OsO_4/NaIO_4$ afforded a mixture of 1-tosyl-2-methoxy-2,3-dihydroindol-3-one (37% yield) and the corresponding 1,2-diol (37% yield).

The reactivity of the ketone function of the 7-azaindolinones **7b-d**, thus obtained, give access to 7-azaindole derivatives substituted in 3-position like 7-azatryptamines.[1] The bromine substituent in 5-position opens new avenue (metallation, Heck reaction) for the development of new active biological products. Furthermore, compounds **4c,d** are of great interest since the indolic analogues[17] unsubstituted in 2-position have been used in the synthesis of Duocarmycin A[17c,e] or Mitomycins.[18] The method here described give an easy and versatile access to 7-azaindole derivatives.

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19. Selected spectra data **4b** and **7b**: **4b**: m.p.: 72 - 74°C (CH_3OH / H_2O) ; I.R. (Kbr) υ = 1650, 920 cm^{-1}; ^1H-NMR ($CDCl_3$, 300Mhz) δ ppm:1.50 (s, 9H, 3 x CH_3), 3.31 (s, 3H, OCH_3), 5.51 (d, 1H, H_{eth}, J = 1.5 Hz), 5.78 (d, 1H, H_{eth}, J = 1.5 Hz), 6.26 (m, 1H, CH), 6.92 (dd, 1H, H_5, J = 5.2, 7.4 Hz), 7.67 (dd, 1H, H_4, J = 1.5, 7.4 Hz), 8.20 (dd, 1H, H_6, J = 1.5, 5.2 Hz). **7b**: m.p.: 58 - 60°C (ether); I.R. (Kbr) υ = 1740, 1680 cm^{-1}; ^1H-NMR ($CDCl_3$, 300Mhz) δ ppm: 1.51 (s, 9H, 3 x CH_3), 3.62 (s, 3H, OCH_3), 5,52 (s, 1H, CH), 7.09 (dd, 1H, H_5, J = 5.2, 7.4 Hz), 7.96 (dd, 1H, H_4, J = 1.5, 7.4 Hz), 8.59 (dd, 1H, H_6, J = 1.5, 5.2 Hz).

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