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THE REACTIONS AND SYNTHESES WITH ORGANOMETALLIC COMPOUNDS. V.

A NEW SYNTHESIS OF INDOLES AND ISOQUINOLINES BY INTRAMOLECULAR PALLADIUM-CATALYZED REACTIONS OF ARYL HALIDES WITH OLEFINIC BONDS

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The synthesis of heterocyclic compounds by utilization of organometallic compounds such as nickel or palladium complexes have been recently studied in this laboratory.[1] The palladium-catalyzed reactions seemed to be particularly fascinating, since a number of different nucleophiles are known to react with olefinic compounds to afford the useful addition products as are seen in the Wacker process and the recent numerous publications,[2] among which Heck et al. revealed that the aryl and vinylic halides react with olefins to afford vinylic derivatives in good yields.[3] However, the reactions catalyzed with palladium in this manner had not been applied to the synthesis of heterocycles. We report in this communication a new synthesis of indole and isoquinoline derivatives by the intramolecular palladium-catalyzed reactions of the aryl halide with an olefinic bond.

The compound(1, X=Br) which was prepared from 2-bromo-N-acetylaniline and methyl-γ-bromocrotonate was adopted as a starting material. When 1 (X=Br) was treated with a catalytic amount of $Pd(OAc)_2$(2 mol%) and PPh_3(4 mol%) in the presence of tetramethylethylenediamine(TMED, 200 mol%) under the stream of nitrogen at 125° for 5.5 hr, methyl 1-acetyl-3-indolyl acetate(2) was obtained in the yield of 43.0% along with acetanilide(4, 15.0%). The former(2) was quantitatively converted to indolyl-3-acetic acid[mp 164-166° (lit.[4] mp 164-166°)] on treatment with 5% NaOH-EtOH at room temperature.

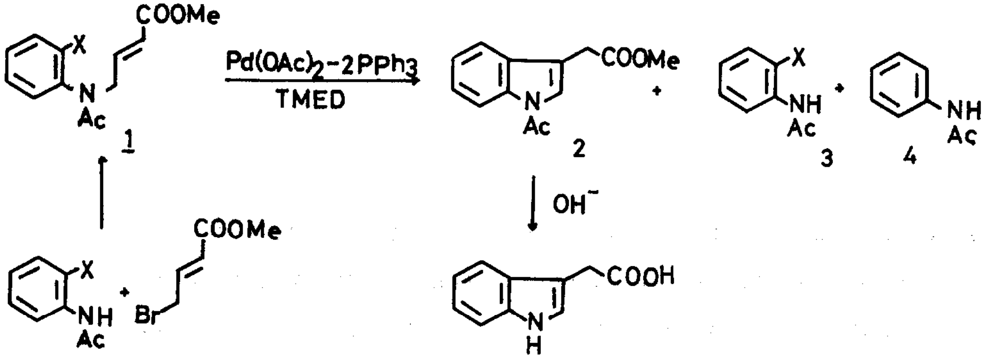


Table 1

Run	X	PPh_3 (mol%)	TMED (mol%)	Temp. (°)	Time (hr)	Products (%)			
						2	3	4	1
1	Cl	4	200	125	5	trace	59	-	10
2	Br	4	200	125	5	32-43	20-29	13-16	~7
3	I	4	200	125	3	20-24$^{a)}$	47	4	4
4	Br	4	100	125	5	30	30	19	4
5	Br	4	400	125	2	-	73	-	27
6	Br	0	200	125	5	25$^{a)}$	49	11	12
7	Br	8	200	125	5	13	54	13	7
8	Br	4	200	80	6	8	64	3	15
9	Br	4	$NaHCO_3$$^{b)}$ 120	130	3	37	-	6	-

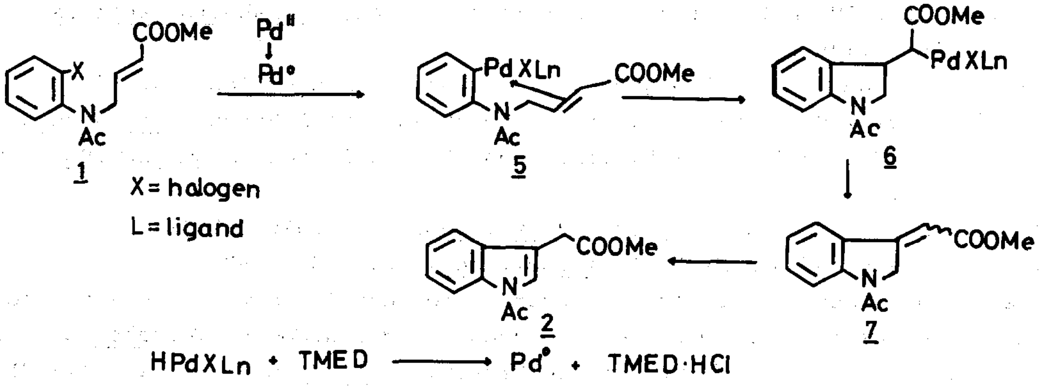
All reactions were carried out with 2 mol% of $Pd(OAc)_2$.

a) The compound(2) was found to contain a movable amount of the tautomeric isomer(7) judging from the n.m.r. spectra.

b) Dimethylformamide(DMF) was used as a solvent and sodium bicarbonate was used as a base instead of TMED.

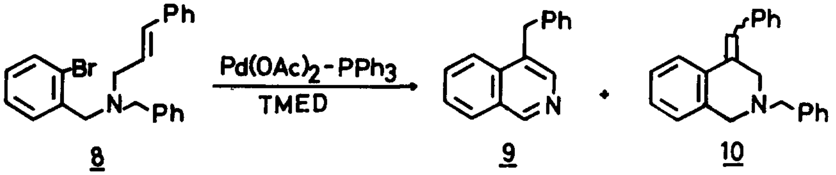
Although the aryl iodide is generally most effective in the oxidative insertion of the metallic compound to the aryl halide, the aryl bromide(1, X=Br) provided a better result in the present cases, whereas the aryl chloride (1, X=Cl) did not give the corresponding cyclized product(2) at all. In all experiments, a base was necessary for regeneration of zerovalent palladium from hydridopalladium complex($HPdXL_2$), for which the present base(TMED) was an appropriate one, because it was readily removed on distillation under reduced pressure after the reactions. The optimum ratio of the base to the substrate was about 2:1 for promotion of the reaction. When the base was in excess more than 2 mol equivalents, any cyclized product was not isolated, but the reason was not clear. Dimethylformamide(DMF) was proved to be a good solvent,[5] since the unfavored deallylation product(3) was not detected in this case.

The plausible mechanism of the present reaction may be regarded as follows. The palladium(II)-complex[$Pd(OAc)_2(PPh_3)_2$] was first converted to zerovalent palladium(PdL_n) by reductive action of the olefinic moiety of 1 associated with the attack of a nucleophile, in which palladium(0) was oxidatively inserted to the aryl bromide, forming the palladium(II)-complex(5). The internal rearrangement of palladium from the phenyl ring to the olefinic carbon took place to generate the σ-complex(6), from which the hydridopalladium halide part was eliminated to form 7, being easily isomerized to the final product(2). The hydridopalladium halide finally generated palladium(0) by action of a base(TMED or $NaHCO_3$) to prevent accumulation of HX, which was available to go through another reaction cycle.



The present reaction must be very useful and valuable, because palladium acetate[$Pd(OAc)_2$] is required only in a catalytic amount(1-2 mol%). Moreover, as the cyclization should take place at the position of the halogen atom present in the original aromatic halide, the synthesis of many indole derivatives with various substituents at the definite position could be possible.

Subsequently, the reaction was further developed to the synthesis of other heterocycles. For example, when the compound(8) was heated with $Pd(OAc)_2$(2 mol %) and PPh_3(4 mol%) in the presence of TMED under the stream of nitrogen at 125° for 69 hr, 4-benzylisoquinoline[9, mp 116-118° (lit.[6] mp 119°)] was obtained in 27.3% yield along with 4-benzylidene derivative(10, 7.6%).



Further studies are in progress for exploitation of the new synthetic method of other heterocycles.

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