

SYNTHESIS OF DERIVATIVES OF INDOLE AND QUINOLINE BY THE
INTRAMOLECULAR CATALYTIC CYCLIZATION OF ALLYLANILINES

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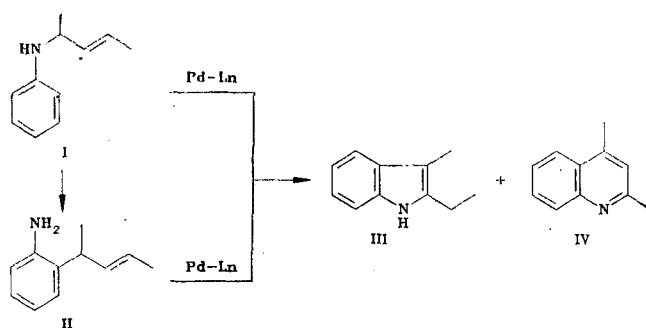
An effective method for the isolation of 3-methyl-2-ethylindole and 2,4-dimethylquinoline by the intramolecular cyclization of N-(1-methyl-2-butenyl)- and 2-(1-methyl-2-butenyl)anilines under the action of the catalyst $\text{PdCl}_2 (\text{DMSO})_n$ was developed. The influence of the nature of the solvent, the temperature, and the concentration of the catalyst on the yield and the ratio of the reaction products was investigated.

According to the data of the work [1], the application of complexes of transition metals in the chemistry of heterocycles permitted the development of a series of original and promising methods for the synthesis of derivatives of indole and quinoline with the utilization of compounds of Ni and Pd. Isoquinolines were obtained by the intramolecular cyclization of 2-allylbenzamides under the action of the catalytic system $\text{PdCl}_2 (\text{CH}_3\text{CN})_2\text{-NaH}$, and 2-alkylindoles were synthesized in sufficiently high yields from 2-allylanilines [2, 3]. By analogy, 2-chloro-N-methyl-N-allylaniline is converted to 1,3-dimethylindole in the presence of stoichiometric amounts of $\text{Ni}(\text{PPh}_3)_4$ [4].

Regrettably, the accomplishment of these reactions requires a large amount of the catalyst or stoichiometric amounts of the complexes of the indicated metals.

With the object of the development of highly active complex catalysts permitting the isolation of substituted indoles and quinolines from available allylanilines, we studied the reaction of intramolecular cyclization taking, as an example, N-(1-methyl-2-butenyl)aniline (I) and 2-(1-methyl-2-butenyl)aniline (II) with the participation of palladium salts in different solvents. Preliminary experiments showed that the most active of the tested complexes of the transition metals (Fe, Co, Ni, and Pd) in the indicated reaction are the catalysts based on PdCl_2 modified by DMSO.

Thus, N-(1-methyl-2-butenyl)aniline (I), as a solution in nitrobenzene, gives a mixture of 2-ethyl-3-methylindole (III) and 2,4-dimethylquinoline (IV) by the action of catalytic amounts of the complex $\text{PdCl}_2\text{-(DMSO)}_n$ at a temperature of 170°C in the course of 2 h; the proportion and the yield of the products change noticeably with the nature of the solvent, the reaction conditions, and the concentration of the catalyst.



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TABLE 1. Influence of the Reaction Temperature on the Ratio of the Products of the Intramolecular Cyclization of Compound II*

T, °C	Time of reaction, hours	Yield, %	T, °C	T, °C	Ratio of (IV)/(III), %	Yield, %	Ratio of (IV)/(III), %
140	9	76	52/48	180	0,6	68	79/21
150	4	61	67/33	190	0,5	67	63,5/36,5
160	3	59	63/37	200	0,3	79	56/44
170	2	81	46/54				

*The reaction conditions were as follows: catalyst PdCl_2 (DMSO)_n, solvent nitrobenzene, and 10:1 molar ratio of the aniline II to the catalyst.

TABLE 2. Influence of the Nature of the Compounds of the Catalytic System on the Yield and Composition of the Products of Cyclization of the Allylaniline II*

Solvent	Modifying additive	Total yield, %	Composition of the reaction products, %	
			III	IV
Nitrobenzene	—	69	43	57
DMSO	—	30	58	42
Benzonitrile	—	15	35	65
DMF	—	Traces	—	—
Nitrobenzene †	DMSO	81	54	46
Benzonitrile	CH_3CN	65	41	59
THF	$\text{Ni}(\text{acac})_2$	68	61	39
DMF	DMSO	15	48	52
	DMSO	10	55	45

*The reaction temperature was 170°C; the duration of the reaction was 2 h.

†The duration of the reaction was 1.5 h.

TABLE 3. Influence of the Concentration of the Catalyst on the Yield and Ratio of the Products of the Intramolecular Cyclization* of the Allylaniline II to the Compounds III and IV

Molar ratio of (II) to the catalyst	Time of reaction, h	Conversion, %	Yield, %	Ratio of the products (III)/(IV), %
10:1	2	92	81	54/46
25:1	2	82	76	60/40
50:1	2	68	49	66/34
100:1	2	22	20	78/22

*The reaction conditions were as follows: temperature 170°C, solvent nitrobenzene, and catalyst PdCl_2 (DMSO)_n.

As can be seen from Table 1, the yield of the compounds III and IV increases on raising the reaction temperature, reaching ~80% at 200°C after 0.3 h. There is little change in the ratio of the compounds III and IV with the conditions of the reaction. In passing from nitrobenzene to DMSO and DMF, the yield of the mixture of III and IV decreases from 69 to 15% (Table 2).

The concentration of the catalyst shows a significant influence on the total yield of the indole III and the quinoline IV and on their ratio. For example, the maximal yield of the products of the intramolecular cyclization of the amine I to the compounds III and IV was obtained under the conditions of a (10-25):1 ratio of the amine to the catalyst, a temperature of 170°C, and the duration of 2 h.

Under analogous conditions, 2-(1-methyl-2-butenyl)aniline (II), which is the product of the Claisen rearrangement of compound I, is readily converted to a mixture of the indole III and the quinoline (IV) in yields which are close to quantitative (Table 3). On the basis of the experimental data, it was concluded that the rearrangement of the allylaniline I to compound II proceeds initially in the conditions of our experiments; the intramolecular cyclization of the latter under the action of catalytically active complexes of palladium then also leads to the formation of the molecules of III and IV.

Therefore, the investigation of the intramolecular cyclization of derivatives of N-allyl- and 2-allylanilines by the action of homogeneous palladium catalysts permitted the development of an effective and promising route for the synthesis of substituted quinolines and indoles which are not readily available.

EXPERIMENTAL

The IR spectra were taken on a UR-20 (film) instrument. The PMR spectra were taken on a Tesla BS-487 (60 MHz) instrument in CCl₄ with an internal standard of TMS. The TLC and column chromatography were performed on Al₂O₃ of the II degree of activity with the eluent of benzene. The GLC analysis was performed on a LKhM-8MD chromatograph using a column 2700 by 3 mm with 5% SE-30 on Chromaton N-AW-DMCS; the flow rate of helium was 40 ml/min. The initial substances were obtained according to the methods of [5].

General Methods of Conducting the Experiment. Into a finger-shaped autoclave (V = 17 cm³) were placed 0.1 g (0.62 mmole) of compound I or II and 0.062 mmole of the complex PdCl₂-Ln (Ln = DMSO, CH₃CN, or DMF). We added 2 ml of the solvent, bubbled the mixture through with argon, and thermostatted it for the required time at the given temperature. The reaction mixture was filtered through a layer of Al₂O₃, 33 by 150 mm, eluting with benzene. The eluent was then distilled, and the residue was analyzed by the method of GLC after first adding the calculated amount of hexadecane as the internal standard. The results of the experiments are presented in Tables 1-3. Reaction products were separated by chromatography on Al₂O₃.

3-Methyl-2-ethylindole (III). This had mp 66°C. The IR spectrum had: 754 (Ar), 1380, 1470 (CH₃), and 3396 cm⁻¹ (N-H). The PMR spectrum had δ values of 1.05 (3H, triplet, CH₃), 2.13 (3H, singlet, CH₃), 2.48 (2H, quartet, CH₂), and 6.80-7.50 ppm (4H, multiplet, ArH).

2,4-Dimethylquinoline (IV). This had n_D^{20} 1.6030 and bp 110°C (2 mm). The IR spectrum: 860, 1600, 3040, 3070 (Ar), 1370, 1380, and 1460 cm⁻¹ (CH₃). The PMR spectrum had δ values of 2.24 (3H, singlet, CH₃), 2.42 (3H, singlet, CH₃), 6.66 (1 H, singlet, Ar-H), and 7.30-7.80 ppm (4H, multiplet, ArH).

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