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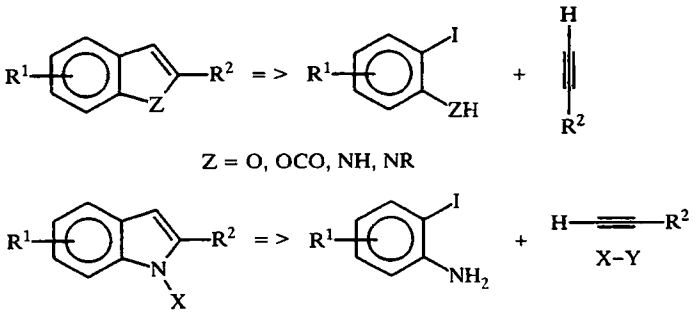
SYNTHESIS OF 2-PHENYLINDOLE N-DERIVATIVES UNDER CONDITIONS OF CATALYSIS BY PALLADIUM COMPLEXES

A. I. Roshchin and N. A. Bumagin

The synthesis of 2-phenylindole N-derivatives was accomplished. The synthesis included the catalytic coupling of o-iodoaniline with phenylacetylene leading to 2-aminotolan, the preparation of the derivative of the last at the nitrogen atom, and its catalytic cyclization to the corresponding indole.

The reaction of aryl halides with terminal acetylenes catalyzed by palladium and copper(I) is a highly effective method for producing a new C—C bond [1]. When a nucleophilic group (OH, COOH, NH_2) is present in the *o*-position of the aryl halide, the compounds formed have the tendency for the intramolecular addition reaction leading to heterocycles such as benzofurans [2], phthalides and isocoumarins [3, 4], and indoles [5-8]. With the exception of the last case, the cyclization already occurs by the action of the $PdCl_2(Ph_3P)_2$–CuI–Et_3N catalytic system, which is usually applied in the acetylene condensation. The cyclization of *o*-alkynylanilines to 2-substituted indoles is accomplished by the action of sodium ethoxide in alcohol or catalytically in the presence of a Pd(II) salt in acetonitrile [9]. Retrosynthetic analysis of the synthesis of heterocycles by means of the catalytic hetero-ring formation of terminal acetylenes can be presented by the following scheme.



Since the catalytic reactions employed permit the widest range of functional groups, such an approach has potential commonality for the synthesis of indoles containing substituents in the benzene ring and the position 2. Taking into account the availability of N-derivatives of *o*-alkynylanilines, the synthesis of N-substituted indoles is possible. Meanwhile, only the simplest N-substituents – Me, Et, Ac [6], Ms [8] (in the last case cyclization proceeds simultaneously with the formation of the C—C bond) – are encountered in published examples.

The given communication is dedicated to the catalytic synthesis of indoles containing different substituents at the nitrogen atom using the example of a simple model system – the cyclization of N-derivatives of 2-aminotolan.

M. V. Lomonosov Moscow State University, Moscow 119899, Russia. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 194-198, February, 1999. Original article submitted February 9, 1998.

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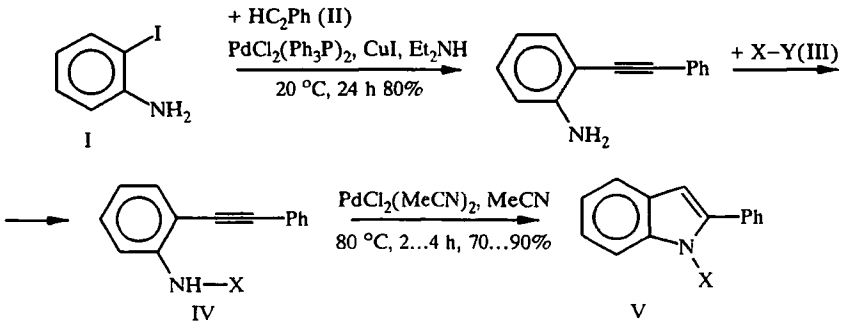


I IV V

X = Ac, Ph_2CHCO, PhNHCO, p-BrC_6H_4CO, PhtN–CH_2;
Y = OAc, Cl, OH

We found, in fact, that the high effectiveness of the addition of N-nucleophiles, catalyzed by Pd(II), to the triple bond allows the cyclization to be accomplished with the participation of various amide groups including those which show very low nucleophilicity and are incapable of the addition under conditions of the normal Michael reaction (Table 1). The cyclization of the N-substituted aminotolans (IVa-f) to the corresponding indoles (Va-f) proceeds smoothly in boiling acetonitrile in the presence of 5 mole % of $PdCl_2(MeCN)_2$ in an atmosphere of argon.

In spite of significant difference in basicity, the compounds (IVa) and (IVc-f) possess comparable reactivity; the acetyl and succinoyl derivatives (IVb) and (IVg) react much worse. The reasons for such behavior are not completely clear, although it is probably associated with the balance of the amide group coordination capacity in relation to palladium and the nucleophilicity of the nitrogen atom in relation to the carbon fragment. We will note that the nonuniform influence of the substituents on reactivity is also observed in the related reaction – the Pd(II)-catalyzed oxidative cyclization of 2-allylphenols to benzofurans [15].

An alternative synthesis of N-substituted indoles, based on catalytic cyclization, is characterized by significantly milder conditions than the direct alkylation or acylation of the indole nitrogen (the production of the N-anion is not required, and the problem of the ambidentate character is absent); it moreover allows the synthesis of compounds with substituents, for which the direct introduction into the indole nucleus is problematic, as in the case of the phthalimidomethyl derivative (Vf). At the present time, further study of the synthetic possibilities of the method is being carried out.

TABLE 1. Synthesis of 2-Aminotolan Derivatives (IV) and their Pd(II)-Catalyzed Cyclization to N-Substituted Indoles (V)

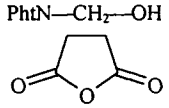
IV	Reagent X-Y	Yield of derivative (IV), %	X	Time of cyclization, h	Yield of indole (V), %
a	—	—	H	2	80
b	Ac_2O	83	Ac	24	17
c	$Ph_2CHCOCl$	85	Ph_2CHCO	6	78
d	PhNCO	75	PhNHCO	4	92
e	p-BrC_6H_4COCl	85	p-BrC_6H_4CO	4	75
f	PhtN—CH_2—OH	40	PhtN—CH_2	2	75
g		75	$HO_2CCH_2CH_2CO$	24	~0

TABLE 2. PMR Spectral Characteristics of 2-Aminotolan Derivatives (IV) and N-Substituted Indoles (V)

Compound	Empirical formula	Found, % / Calculated, %			Substituent at N	mp, °C	Solvent	PMR spectrum (300 MHz; chemical shifts, δ, ppm; J, Hz)	
		C	H	N				Ar-H	other protons
IVa	$C_{14}H_{11}N$	—	—	—	H	89...90	Acetone-d_6	6,59...6,64 (m, 2H); 7,04 (td, 1H) 7,22...7,27 (m, 3H); 7,28 (d, 1H); 7,41 (d, 1H) 7,44 (m, 1H)	4,17 (br. s, 2H, NH_2)
IVc	$C_{28}H_{21}NO$	87,10 / 86,79	5,63 / 5,46	3,60 / 3,61	$COCHPh_2$	135	$CDCl_3$	7,12 (t, 1H, J = 7,6); 7,21 (t, 2H, J = 7,2) 7,27...7,43 (m, 14H); 7,49 (dd, 1H, J = 7,7; 1,3) 8,56 (d, 1H, J = 8,4)	5,21 (s, 1H, CH); 8,25 (br. s, 1H, NH)
IVd	$C_{21}H_{16}N_2O$	80,41 / 80,75	5,00 / 5,16	8,77 / 8,97	CONHPh	192 (dec.)	$CDCl_3$	7,07 (m, 2H); 7,24...7,56 (m, 12H) 8,29 (d, 1H, J = 8,1)	6,66 (s, 1H, NH)
IVe	$C_{21}H_{14}NOBr$	67,32 / 67,04	4,04 / 3,75	3,65 / 3,72	COC_6H_6Br	147	DMSO-d_6	7,29 (t, 1H, J = 7,5); 7,41...7,46 (m, 6H) 7,62 (d, 1H, J = 7,9); 7,73...7,75 (d, 3H) 7,97 (d, 2H, J = 8,5)	9,98 (br. s, 1H, NH)
IVf	$C_{23}H_{16}N_2O_2$	78,41 / 78,39	4,54 / 4,58	7,95 / 7,95	CH_2NPht	175...176	DMSO-d_6	6,70 (t, 1H, J = 7,4); 7,08 (d, 1H, J = 8,3) 7,24 (t, 1H, J = 8,0); 7,43...7,62 (m, 5H) 7,84...7,86 (m, 5H)	5,23 (d, 2H, CH_2) 6,00 (br. s, 1H, NH)
IVg	$C_{18}H_{15}NO_3$	73,32 / 73,71	5,04 / 5,15	4,65 / 4,78	$COCH_2$— CH_2CO_2H	187...189	DMSO-d_6	7,18 (t, 1H, J = 7,3); 7,39 (td, 1H, J = 7,8; 1,2) 7,43...7,47 (m, 3H); 7,55 (dd, 1H, J = 7,8; 1,2) 7,62...7,65 (m, 2H); 7,83 (d, 1H, J = 8,2)	2,56 (t, 2H, CH_2CON, J = 6,7) 2,70 (t, 2H, CH_2CO_2H, J = 6,7) 9,4 (s, 1H, NH)
Vb	$C_{16}H_{13}NO$	—	—	—	Ac	Oil	Acetone-d_6	6,70 (s, 1H, 3-H); 7,30 (m, 2H); 7,54 (m, 6H) 8,29 (d, 1H, J = 8,3)	2,07 (s, 3H)
Vc	$C_{28}H_{21}NO$	86,50 / 86,79	5,35 / 5,46	3,50 / 3,61	$COCHPh_2$		DMSO-d_6	6,78 (s, 1H, 3-H); 6,93...6,96 (m, 4H) 7,18...7,24 (m, 6H); 7,27 (d, 1H, J = 7,8) 7,34 (td, 1H, J = 7,7; 1,1); 7,55 (s, 5H) 7,57 (d, 1H, J = 8,0); 8,15 (d, 1H, J = 8,2)	5,30 (s, 1H, CH)
Vd	$C_{21}H_{16}N_2O$	80,45 / 80,75	5,09 / 5,16	8,89 / 8,97	CONHPh	121	DMSO-d_6	6,91 (s, 1H, 3-H); 7,11...7,47 (m, 9H) 7,56 (t, 3H, J = 6,9); 7,67 (t, 2H, J = 6,8)	10,72 (s, 1H, NH)
Ve	$C_{21}H_{14}NOBr$	67,09 / 67,04	4,04 / 3,75	3,58 / 3,72	COC_6H_4Br	61	Acetone-d_6	6,87 (s, 1H, 3-H); 7,15...7,80 (m, 13H)	—
Vf	$C_{23}H_{16}N_2O_2$	78,36 / 78,39	4,52 / 4,58	7,83 / 7,95	CH_2NPht	162	DMSO-d_6	6,53 (s, 1H, 3-H); 7,11 (m, 2H) 7,44...7,65 (m, 7H); 7,79 (m, 4H)	6,04 (s, 2H, CH_2)

EXPERIMENTAL

The NMR spectra were recorded on the Bruker AM-300 instrument, and the chemical shifts are presented relative to TMS. Data of the elemental analysis (for compounds synthesized for the first time), melting temperatures, and PMR spectra are presented in Table 2.

The N-(hydroxymethyl)phthalimide was obtained by the method from the work [10].

2-Aminotolan (IVa). We improved somewhat the method proposed in the work [5] for the reaction of *o*-iodoaniline with trimethylsilylacetylene. To mixture of 0.078 g (0.3 mmol) of $PdCl_2(MeCN)_2$, 0.314 g (1.20 mmol) of triphenylphosphine, and 0.287 g (1.50 mmol) of CuI 5.0 ml of DMF are added, and the mixture is stirred for 15 min. Solution of 33.0 g (150 mmol) of *o*-iodoaniline in 100 ml of diethylamine and 22.0 ml (200 mmol) of phenylacetylene is then added. The resulting solution is stirred in argon atmosphere at room temperature. After 15 min, the mixture is heated to boiling; outer cooling with water is required. The stirring is continued for a night, and then the reaction mixture is poured into 300 ml of water. The reaction product initially comes off as an oil and is crystallized shortly after; it is filtered off, dried in air, and crystallized from the mixture of hexane–ethyl acetate. The yield is 23.2 g (80%), mp 89-90°C; according to reference data [11], mp 89°C. The PMR spectrum is analogous to that presented in the work [12].

Acylation of 2-Aminotolan. General Method. To solution of 1.0 g (5.17 mmol) of 2-aminotolan (IVa) in 10 ml of dioxane or THF 7 mmol of the acylating agent (III) and 10 mmol of pyridine (only in the case of the acid chlorides) are added. The mixture is maintained for 1 h at room temperature; it is then boiled for 5 min, cooled, and poured into 50 ml of water. The solution of K_2CO_3 is added until an alkaline reaction is obtained. The mixture is stirred until the oil hardens. The product of acylation is filtered off and then recrystallized. The following compounds are obtained by the given method. 2-(Acetamido)tolan (IVb), from (IVa) and Ac_2O, with the yield 83%, mp 118-119°C (from ethanol); according to the data of the work [12], mp is 117-118°C. 2-(Diphenylacetamido)tolan (IVc), from (IVa) and $Ph_2CHCOCl$, with the yield 85%, mp 135°C (from toluene). N-(Phenylcarbamoyl)-2-aminotolan (IVd), from (IVa) and PhNCO, with the yield 75%, mp 192°C (decomp.) (from $CHCl_3$). 2-(4-Bromobenzamido)tolan (IVe), from (IVa) and *p*-BrC_6H_4COCl, with the yield 85%, mp 147°C (from ethanol). 2-(Succinoylamido)tolan (IVg), from (IVa) and succinic anhydride, with the yield 75%, mp 187-189°C.

N-(Phthalimidomethyl)-2-aminotolan (IVf). Solution of 1.0 g (5.1 mmol) of aminotolan (IVa) and 0.9 g (5.1 mmol) of N-(hydroxymethyl)phthalimide in 5 ml of alcohol is boiled for 2 h. After cooling the mixture, the precipitated derivative is filtered off. The yield is 0.8 g (40%), mp 175-176°C.

Palladium-Catalyzed Cyclization of N-Acyl-2-aminotolans to Derivatives of Indole. General Method. Solution of 1.0 mmol of the initial compound and 0.013 g (0.05 mmol) of $PdCl_2(MeCN)_2$ in 3 ml of MeCN is boiled in argon atmosphere for several hours until the completion of the reaction (TLC). The acetonitrile is then evaporated. To the residue 5 ml of chloroform are added, and the solution is passed through a layer of silica gel and evaporated. The reaction time and the yields of the indoles are presented in Table 1. The PMR spectra and data of the elemental analysis are presented in Table 2. The following compounds are obtained by the given method. 2-Phenylindole (Va) with the yield 80%, mp 187°C (according to published data [13], mp 190°C). 1-Acetyl-2-phenylindole (Vb) with the yield 17%; it is an oil, and the PMR spectrum corresponds with published data [14]. 1-(Diphenylacetyl)-2-phenylindole (Vc) with the yield 78%. 1-(Phenylcarbamoyl)-2-phenylindole (Vd) with the yield 92%, mp 121°C. 1-(4-Bromobenzoyl)-2-phenylindole (Ve) with the yield 75%, mp 61°C. 1-(Phthalimidomethyl)-2-phenylindole (Vf) with the yield 75%, mp 162°C.

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