7. S. Gronowitz, J. Johnson, and A.-B. Hörnfeldt, Chem. Scr., 7, 76 (1975).
8. W. Hoek, H. Wynberg, and J. Strating, Rec. Trav. Chim., 85, 1054 (1966).

FISCHER LIQUID-PHASE CYCLIZATION OF ARYLHYDRAZONES

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It is known that Fischer cyclization of arylhydrazones to indoles proceeds under the action of acidic agents, in particular, metal chlorides. The acidophobicity of the indoles formed and the tendency of the hydrazones toward resinification in acid medium demand a search for new cyclization agents, and also determination of the factors affecting cyclization in the presence of known catalysts.

In this work, we have investigated cyclization of phenylhydrazones (PH) of acetophenone (PHAP), acetone (PHAC), and acetaldehyde (PHAA) in different solvents (bromobenzene, anisole, diglyme) in the presence of anhydrous $AlCl_3$, $ZnCl_2$, $FeCl_3$, $NiCl_2$, $CoCl_2$ and also laminar graphite compounds (LGC) involving these chlorides. As is evident from Table 1, in the series of studied salts, only the chlorides of zinc and aluminum are active in cyclization of phenylhydrazones, but very strong resinification proceeds in the presence of $AlCl_3$.

In order to determine the nature of the catalytically active centers (the chlorides themselves, or traces of protonic acids formed upon their hydrolysis) we investigated cyclization of phenylhydrazones under the action of zinc chloride in the presence of potassium acetate, which binds the protonic acid within the volume. As is evident from Table 2, addition of AcOK ($ZnCl_2$: AcOK = 1 : 3) insignificantly affects cyclization of PHAA, but completely suppresses cyclization of PHAP. These results show that protonic acids substantially accelerate conversion of easily cyclicized hydrazones (PHAP) to indoles, practically have no affect on the analogous reaction of hydrazones which are difficult to cyclicize (PHAA), and agree with the results of other authors [1] on the preferential role of L centers of aluminum oxide in heterogeneous catalytic cyclization of PHAA.

The nature of the solvent affects the solubility of $ZnCl_2$ and the possibility of its complexation with the solvents. For quantitative experiments, we chose bromobenzene and anisole since the latter, in contrast with diglyme, do not form stable complexes with zinc chloride. In anisole and bromobenzene, $ZnCl_2$ is not completely dissolved even upon boiling. We should note that the solubility of $ZnCl_2$ in anisole sharply increases

TABLE 1. Indolization of Arylhydrazones in the Liquid Phase at 155°C over Metal Chlorides and Their Laminar Graphite Compounds (mole ratio PH/salt = 1 : 1)

Cyclization agent	Yield of indoles, mole fractions of original hydrazone		
	PHAP*	PHAC†	PHAA*
$AlCl_3$, anhydrous	1,00		0,02
CCГ – $AlCl_3$ (52% salt)	0,80	0,10	0,01
$FeCl_3$, anhydrous	Traces	Traces	Traces
CCГ – $FeCl_3$ (50% salt)	»	»	»
$NiCl_2$, anhydrous	»	»	»
CCГ – $NiCl_2$ (35% salt)	»	»	»
$CoCl_2$, anhydrous	»	»	»
CCГ – $CoCl_2$ (50% salt)	»	»	»
$ZnCl_2$, anhydrous	0,65–0,75	0,95	»
CCГ – $ZnCl_2$ (36% salt)	0,65–0,85	0,31	»

*In bromobenzene medium.
†In anisole medium.

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TABLE 2. Relative Role of B and L Acid Centers upon Indolization of Arylhydrazones in the Liquid Phase in Bromobenzene Medium at 155°C

Phenylhydrazone	Mole ratio of PH and $ZnCl_2$, w	Cyclization agent, mole ratio	Indolization of PH aftet 30 min*
PHAA	1	$ZnCl_2$	++
PHAA	1	$ZnCl_2$ + AcOK (1 : 3)	+
PHAP	1	$ZnCl_2$	+++
PHAP	1	$ZnCl_2$ + AcOK (1 : 1)	++
PHAP	1	» (1 : 2)	+
PHAP	1	» (1 : 3)	–
PHAC	2	$ZnCl_2$	++
PHAC	2	$ZnCl_2$ + H_2O (5 : 1)	+++
PHAC	2	$ZnCl_2$ + AcOK (1 : 2)	+

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*Cyclization less than 3% (+), from 3 to 30% (++), and more than 30% (+++).

TABLE 3. Dependence of the Yield of 2-Methylindole on the Mole Ratio of PHAC and $ZnCl_2$ (w) in Cyclization of PHAC in the Presence of $ZnCl_2$ or LGC–$ZnCl_2$ (anisole, 155°C, 1 h)

Cyclization agent	Amount of reagent, moles		w	Yield of MI, mole fractions	
	PHAC	$ZnCl_2$		PHAC	$ZnCl_2$
Fused $ZnCl_2$	0,0211	0,0211	1	0,96	0,96
» »	0,0210	0,0105	2	0,47	0,94
» »	0,0212	0,0053	4	0,24	0,96
» »	0,0210	0,0021	10	0,09	0,90
Fused $ZnCl_2$ with addition of 0.0022 moles H_2O	0,0210	0,0106	2	0,41	0,82
$ZnCl_2$ dried in stream of Cl_2	0,0212	0,0106	2	0,45	0,90
Fused $ZnCl_2$	0,0212	0,0424	0,5	0,28	0,14
LGC– $ZnCl_2$ (31% salt)	0,0210	0,0210	1	0,31	0,31
LGC– $ZnCl_2$ (36% salt)	0,0210	0,0105	2	0,16	0,32

TABLE 4. Gas–Liquid Chromatography Analysis of the Reaction Mass upon Cyclization of PHAC in the Liquid-Phase in Anisole Medium at 155°C and Mole Ratio PH: $ZnCl_2 = 1:1$

Cyclization agent	Sample untreated with water		Sample treated with water	
	content, moles/liter			
	PHAC	MI	PHAC	MI
Fused $ZnCl_2$	0,004	0,005	0,006	0,010
» »	0,020	0,007	0,024	0,007
LGC – $ZnCl_2$ (36% salt)	0,015	0,035	0,108	0,044

with addition of PHAC; for the ratio $ZnCl_2$: PHAC = 1 : 4, the amount of undissolved salt is insignificant, while for the ratio $ZnCl_2$: PHAC = 1 : 10 we observe complete dissolution of $ZnCl_2$. An increase in the solubility of $ZnCl_2$ upon addition of phenylhydrazones apparently indicates formation of a complex between the hydrazone and the zinc chloride.

For the case of cyclization of PHAC in the presence of anhydrous $ZnCl_2$, we carried out a study of the basic characteristics of the process (Table 3 and Fig. 1). The reaction was carried out in boiling anisole and the products were analyzed by the gas–liquid chromatography method. We found that the composition of the reaction mass depends on the mole ratio of PHAC and $ZnCl_2$ (w). Thus when w = 1, the reaction mixture contains 2-methylindole (MI) and unreacted PHAC. When w > 1, aniline is also present in solution along with MI and PHAC. This indicates that aminonitrile cleavage of PHAC occurs. And when w < 1, strong resinification of the MI form occurs. For cyclization of PHAC, we need to use stoichiometric amounts of $ZnCl_2$. This is con-

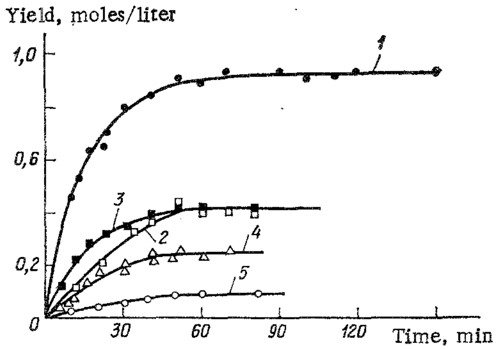
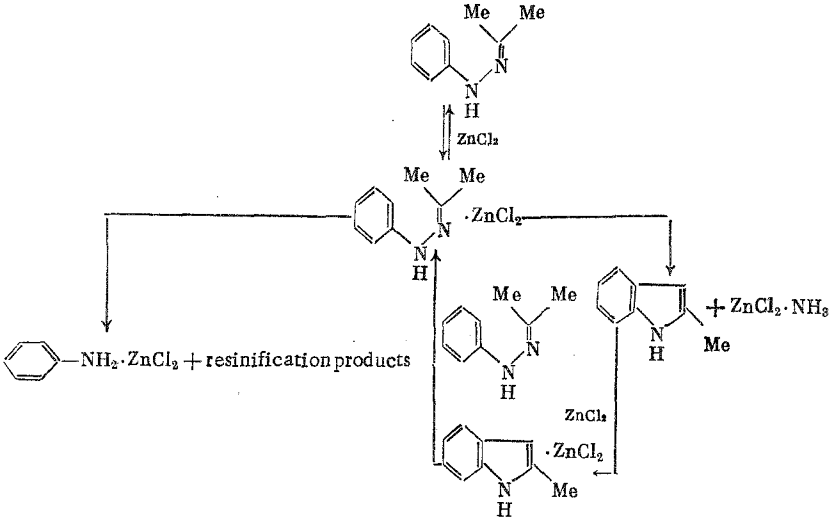


Fig. 1. Yield of 2-methylindole (mole fractions of the starting PHAC) in cyclization in anisole medium (155°C) as a function of the mole ratio of PHAC and $ZnCl_2$ (w), equal to: 1) 1; 2) 2; 3) 2 (with addition of 0.0022 moles H_2O); 4) 4; 5) 10.

nected with the fact that the starting and end products have basic character and may form complexes with $ZnCl_2$, deactivating it. The formation of a complex between PHAC and $ZnCl_2$ is indicated by the increase in solubility of $ZnCl_2$ in anisole in the presence of PHAC, and also by the fact that samples of a reaction mass that were untreated with water show an amount of PHAC which is too low and not constant (when $w=1$) in solution. Formation of complexes of $ZnCl_2$ and MI inasmuch have a subsequent increase in reaction mass for a sample treated with water (when $w = 1$) (see Table 4). We should note that the complex $ZnCl_2$ PHAC is more stable than the one with MI, since addition of fresh portions of PHAC to a reaction mass already having achieved equilibrium leads to an increase in the concentration of MI in solution (when $w < 1$). The complexes $ZnCl_2 \cdot NH_3$ and $ZnCl_2 \cdot PhNH_2$ have even greater stability. Neither PHAC or MI displace ammonia and aniline from these complexes. The nature of such stable complexes causes deactivation of $ZnCl_2$ and therefore requires use of an equimolar amount of zinc chloride relative to PHAC. The data obtained allows us to propose a scheme for the process of cyclization of PHAC.

Scheme



It is interesting to compare the activity in PH cyclization of free metal chlorides and laminar graphite compounds (LGC) involving these chlorides. The latter are products of insertion of metal chlorides into the interplanar space of the graphite. In a number of cases, weak interaction of the charge transfer complex type occurs between the carbon framework of the graphite and the salt molecules [2]. This on the one hand may lead to a partial decrease in salt activity, and on the other hand it may facilitate an increase in salt stability relative to the action of nucleophilic reagents. As is evident from Table 1, we observe a correspondence between the activity of the laminar graphite compounds (LGC) with metal chlorides and the salts themselves. Thus, in a number of the investigated laminar graphite compounds, activity in phenylhydrazone cyclization is manifested only by LGC−$AlCl_3$ and LGC−$ZnCl_2$; and in the presence of LGC−$AlCl_3$, as in the case of free $AlCl_3$, we observe strong resinification of the reaction mass. However, in contrast to $ZnCl_2$, LGC−$ZnCl_2$ makes it possible for the reaction to proceed catalytically. The same catalyst works over six cycles, and the overall yield of MI is greater than one mole; it amounts to about four moles per mole $ZnCl_2$ in the LGC. Furthermore, in the presence of LGC−$ZnCl_2$, the reaction mass is significantly less resinified than in the presence of the free salt. It is important to emphasize that LGC−$ZnCl_2$ is a heterogeneous catalyst, since heating the solution separated from the LGC−$ZnCl_2$ in the initial stage of the process does not lead to further cyclization of the phenylhydrazone.

EXPERIMENTAL

Starting Materials. LGC−$AlCl_3$ [2], LGC−$FeCl_3$ [3], LGC−$NiCl_2$, LGC−$CoCl_2$ [4], and LGC−$ZnCl_2$ [5] were obtained as in the cited papers. PHAA, synthesized according to [6], was recrystallized from an alcohol−NH_4OH mixture, mp 100-101°C. PHAC was obtained according to [7, 8], bp 163°C (50 mm). PHAP [8] was recrystallized from alcohol, mp 160°C (anti-isomer).

Gas−liquid chromatography analysis was carried out on a Tsvet-100 chromatograph. For the cyclization products of PHAA: column 2 m × 3 mm; support Chromaton N-AW, phase SE-30, 124°C. For the cyclization products of PHAC: column 1 m × 3 mm, support − silanized Chromaton N-AW, phase − Carbowax-20M, 153°C.

Anlysis of the cyclization products of PHAC was carried out by the PMR method using the protons of the methyl group of the phenylhydrazone (3.71 ppm) on the Perkin-Elmer R-20 spectrometer (60 MHz) with HMDS as the external standard.

General Cyclization Method. To a solution of 3.13 g PHAC in 25 ml anisole, we added 2.8 g $ZnCl_2$ and mixed for two 2 h under a stream of N_2 at 155°C. During the reaction, we extracted samples (0.2 ml) which were washed with water to remove the metal chlorides and analyzed by the gas−liquid chromatography method.

CONCLUSION

1. In the series of chlorides of zinc, aluminum, iron (III), nickel(II), and cobalt(II), zinc chloride is the most active and selective reagent for stoichiometric indolization of phenylhydrazones in the liquid phase.

2. In the presence of laminar graphite compounds, indolization of phenylhydrazones with zinc chloride has a catalytic character.

LITERATURE CITED

1. N. N. Suvorov, N. E. Starostenko, G. V. Antipina, V. Ya. Kanterov, N. Ya. Podkhalyuzina, and O. V. Bulgakov, Zh. Fiz. Khim., 46, 2028 (1972).
2. A. R. Ubbelohde and F. A. Lewis, Graphite and Its Crystal Compounds, Oxford University Press (1961).
3. M. E. Vol'pin, V. E. Prusakov, R. A. Stukan, V. I. Gol'danskii, V. A. Semion, and Yu. T. Struchkov, Zh. Strukt. Khim., 17, 756 (1976).
4. N. D. Lapkina, Yu. N. Novikov, Yu. T. Struchkov, and M. E. Vol'pin, Zh. Strukt. Khim., 11, 1039 (1970).
5. E. Stumpp and E. Werner, Carbon, 4, 538 (1956).
6. E. Fischer, Liebigs Ann. Chem., 342, 25 (1905); J. Chem. Soc., 99, 2085 (1911).
7. E. Fischer, Liebigs Ann. Chem., 236, 126 (1886).
8. R. Reisenegger, Chem. Ber., 16, 662 (1883).