the primary groups in the cellulose carbanilate were tosylated.

This shows 0.90 of the original 1.03 to be primary, and the remaining 0.13 to be secondary. Thus the rate of tritylation is 0.90 × 2/.13, or 13.8 times as fast in the primary as in the average of the secondary positions. These data point to the conclusion that under well-controlled reaction conditions tritylation of cellulose or cellulose derivatives may be effected to cover approximately 90% of the primary hydroxyl groups, with simultaneous reaction to a minor degree with secondary hydroxyl groups.

Acknowledgment.—The authors wish to express their appreciation for the assistance of John T. Clarke in connection with the experimental part of this paper.

Summary

1. Reaction conditions for preparation of cellulose trityl ethers have been studied in detail. Regenerated celluloses provide the most suitable starting materials. Products of from approximately 1.0 to 1.2 trityl groups for each glucose unit readily may be obtained. By proper choice of reaction conditions, very little degradation of cellulose occurs during tritylation.

2. Detritylation by treatment with acid may result in appreciable degradation of the cellulose. This may be largely avoided by use of a solution of hydrochloric acid in an organic solvent.

3. The tritylation reaction has been shown to be 13.8 times as fast with primary as with the average of secondary hydroxyl groups. Under moderate reaction conditions tritylation may be carried out to cover approximately 90% of the available primary hydroxyl groups, with simultaneous reaction to a small degree with secondary hydroxyl groups.

ROCHESTER, N. Y. RECEIVED JUNE 23, 1943

[CONTRIBUTION FROM THE NOYES LABORATORY OF THE UNIVERSITY OF ILLINOIS]

Boron Fluoride as a Condensing Agent in the Fischer Indole Synthesis

BY H. R. SNYDER AND CURTIS W. SMITH

The preparation of indoles from the phenylhydrazones of aldehydes and ketones having an α-methylene group has been carried out with the aid of a number of acidic reagents, but a search of the literature revealed no instance of the use of boron fluoride as the condensing agent. In order to test the value of this reagent in the indole synthesis, a number of phenylhydrazones now have been treated with boron fluoride.

Those phenylhydrazones which have been converted to indoles by the aid of other reagents generally have undergone the reaction under the influence of the new condensing agent. The boron fluoride may be used in various ways. The gas may be bubbled into a solution of the phenylhydrazone in an organic solvent, with subsequent heating of the mixture to bring about decomposition of the phenylhydrazone–boron fluoride compound; if a non-polar solvent is used, this compound may separate as a heavy oil and the decomposition then may be effected by heating the oil either alone or under the solvent. Another technique consists in bubbling boron fluoride through a refluxing solution of the phenylhydrazone in a solvent such as benzene or xylene. Boron fluoride etherate may be employed to advantage, since the liquid etherate can be handled more conveniently than the gaseous boron fluoride. The phenylhydrazones, being stronger bases than ether, react with the etherate to form the phenylhydrazone–boron fluoride complexes and the liberated ether can be removed by distillation. The use of the liquid etherate permits convenient and accurate measurement of the amount of boron fluoride, an excess of which is to be avoided.

The formation of the phenylhydrazone–boron fluoride complexes is only slightly exothermic, and their decomposition in the presence of solvents proceeds smoothly; the decomposition in the absence of solvents may be so violent as to be mildly explosive. Acetic acid appears to be the best solvent for the reaction. For example, the decomposition of the complex of boron fluoride with the phenylhydrazone of methyl ethyl ketone, carried out in refluxing acetic acid, produced 2,3-dimethylindole in 85% yield; decomposition in refluxing ethanol gave a 69% yield and decomposition in the absence of a solvent gave only a 50% yield.

The yields of the various indoles prepared by the use of boron fluoride are shown in the accompanying table, along with the best yields reported in preparations carried out with other condensing agents. With few exceptions the yields obtained with boron fluoride are comparable to those of other procedures. A notable exception is the preparation of 2-methylindole from acetone phenylhydrazone; none of the product was obtained from the attempts with boron fluoride, although it has been prepared in 60% yield with zinc chloride. It is not surprising that the synthesis of indole from acetaldehyde phenylhydrazone failed, since this transformation apparently has not been carried out with any of the condensing agents. The synthesis of 2-carbethoxyindole-3-acetonitrile apparently is an unusually difficult preparation also. Alcoholic sulfuric acid is reported to be ef-

TABLE I

CONVERSION OF PHENYLHYDRAZONES TO INDOLES

		Condensations with boron fluoride etherate		Other condensing agents		
Phenylhydrazone of	Product	Solvent	Yield, %	Reagent (and solvent)	Yield, %	Reference
Acetaldehyde	(Indole)	*a*	0	ZnCl	0	1
Acetone	2-Methylindole	*b*	0	$ZnCl_2$	60	1
				$ZnCl_2$(methylnaphthalene)	80	2
Methyl ethyl ketone	2,3-Dimethylindole	None	50	$NiCl_2$ (cat. amt.)	65	3
		C_2H_5OH	69			
		CH_3CO_2H	85	$ZnCl_2$	45	1
Isovaleraldehyde	3-Isopropylindole	CH_3CO_2H	60	$ZnCl_2$	38	4
Acetophenone	2-Phenylindole	*c*, C_6H_5	67.5	$ZnCl_2$	80	5
Propiophenone	2-Phenyl-3-methylindole	CH_3CO_2H	87	Cu_2Cl_2 (cat. amt.)	72.5	6
				HCl(C_2H_5OH)		7
Ethyl pyruvate	Indole-2-carboxylic acid[d]	None	7.4	$ZnCl_2$	6[e]	1, 8
				$ZnCl_2$(methylnaphthalene)	60[e]	2
Ethyl levulinate	2-Methylindole-3-acetic acid[d]	None	96	$SnCl_2$		9
				$ZnCl_2$	33[e]	1, 8
α-Keto-γ-butyrolactone	Lactone of 3-methylolindole-2-carboxylic acid	*c*, C_2H_5OH	21.6	HCl(CH_3CO_2H)	33	10
		CH_3CO_2H	57.5[f]			
Ethyl α-keto-γ-cyanobutyrate	(2-Carbethoxyindole-3-acetonitrile)	*g*	0[h]	H_2SO_4(C_2H_5OH)	[i]	11
Cyclopentanone	Dihydropentindole	CH_3CO_2H	41	C_6H_5MgBr	"Poor"	12
				H_2SO_4	45	13
Cyclohexanone	1,2,3,4-Tetrahydrocarbazole	CH_3CO_2H	93	H_2SO_4	93	14
α-Methylphenylhydrazone of cyclohexanone	N-Methyl-1,2,3,4-tetrahydrocarbazole	CH_3CO_2H	84	H_2SO_4, CH_3CO_2H		15

[a] Experiments were run in the presence of benzene and without solvent. [b] Experiments were run without solvent and in xylene, acetic acid and propionic acid. From the run in propionic acid an unidentified substance of m. p. 137° was obtained; *anal.:* C, 51.96; H, 6.56; N, 9.30. [c] Boron fluoride, rather than the etherate, was used. [d] The crude product was saponified. [e] The product was isolated as the ester. [f] About 10% of the phenylhydrazone was isolated as the lower-melting isomer, m. p., 100.5°. *Anal.* Calcd. for $C_{10}H_{10}N_2O_2$: C, 63.32; H, 5.30; N, 14.70. Found: C, 63.15; H, 5.20; N, 15.21. [g] Experiments were run with xylene, acetic acid and propionic acid as solvents. [h] The phenylhydrazone recovered from the run in xylene was isomeric with that used initially. The new phenylhydrazone melted at 84.5°. *Anal.* Calcd. for $C_{13}H_{15}N_3O_2$: C, 63.66; H, 6.17. Found: C, 63.88; H, 6.61. [i] The product isolated was not the nitrile but the acid.

fective in bringing about the ring closure, but with simultaneous hydrolysis of the nitrile group; boron fluoride was entirely ineffective. For those indole syntheses in which it is effective boron fluoride appears to be a superior condensing agent because of the ease with which the product can be isolated. The ammonia–boron fluoride, produced along with the indole, is insoluble in the solvents used for the reaction and hence can be removed by filtration; the indole often can be obtained by merely allowing it to crystallize from the mother liquor.

The appearance of a deep color in the reaction mixtures, noted by many investigators using various condensing agents, was observed also in the preparations with boron fluoride. The color has been attributed to the formation of resinous by-products[16] but it has been pointed out that this suggestion is not tenable because of the fact that the color fades as the reaction proceeds and also because the appearance and disappearance of the color are observed even though no by-products can be detected.[17] A more probable explanation of the color phenomena may be based on an equilibrium between the colorless phenylhydrazone and the colored phenylazo tautomer, represented in the diagram as the boron fluoride complexes I and II.

If the color is due to the phenylazo compound, then it should not be observed in reactions of α-substituted phenylhydrazones. Mention of the color always has been made in connection with reactions of unsubstituted phenylhydrazones, but no statement of its absence in condensations of the substituted compounds has come to the writers' attention. The condensation of cyclohexanone α-methylphenylhydrazone was carried out to test the color development with a substituted phenylhydrazone. Although the deepest color in any of the boron fluoride condensations was observed with cyclohexanone phenylhydrazone, no intense color developed during the condensation of the α-methyl derivative.

The equilibrium between the forms I and II also may account for the isomerization of phenyl-

(1) Fischer, *Ann.*, **236**, 116 (1886); *Ber.*, **19**, 1563 (1886); **21**, 1071, 1811 (1888).

(2) German Patent 238,138; *Frdl.*, **10**, 332 (1910–1912).

(3) Korczynski and Kierzek, *Gazz. chim. ital.*, **55**, 361 (1925).

(4) Trenkler, *Ann.*, **248**, 107 (1888).

(5) "Organic Syntheses," John Wiley and Sons, Inc., New York, N. Y., 1942, Vol. 22, p. 98.

(6) Arbusov, Zaitzev and Razumov, *Ber.*, **68**, 1792 (1935).

(7) Plant and Tomlinson, *J. Chem. Soc.*, 955 (1933).

(8) German Patent 38,784; *Frdl.*, **1**, 151 (1877–87).

(9) Kögl and Kostermaus, *Z. physiol. Chem.*, **235**, 201 (1935).

(10) Lions and Harradence, *J. Proc. Roy. Soc. N. S. Wales*, **72**, 221 (1938).

(11) Keimatsu and Sugasawa, *J. Pharm. Soc. Japan*, **48**, 755 (1928).

(12) Grammaticakis, *Compt. rend.*, **209**, 317 (1939).

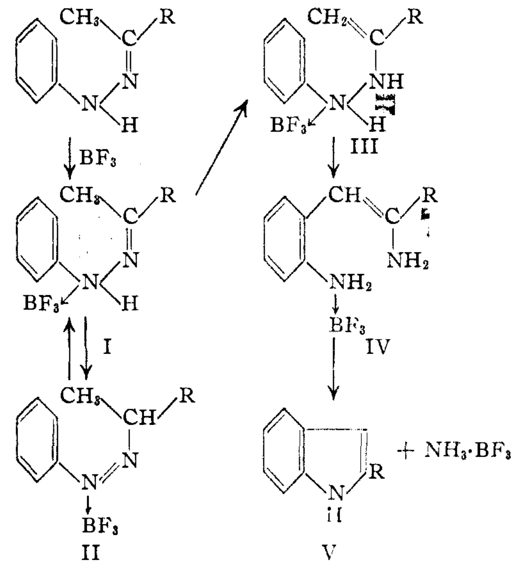
(13) Perkin and Plant, *J. Chem. Soc.*, **123**, 3245 (1923).

(14) Hoshino and Takiura, *Bull. Chem. Soc., Japan*, **11**, 218 (1936).

(15) Perkin and Plant, *J. Chem. Soc.*, **119**, 1825 (1921).

(16) Reddelien, *Ann.*, **388**, 179 (1912).

(17) Bodforss, *Ber.*, **58**, 775 (1925).



hydrazones which has been noted occasionally in unsuccessful or partly successful Fischer syntheses. The two isomers are assumed to be the *syn* and *anti* phenylhydrazones. The interconversion of forms I and II would provide ample opportunity for the formation of the *anti*-methyl isomer from the *syn*-methyl compound (I) or for the reverse change. Since the configuration of the stable boron fluoride complex (I) is not necessarily that of the stable phenylhydrazone, it might be expected that some stable phenylhydrazones could be converted to the labile isomers by the process indicated. Reversibility of the change of I to III[18] also would provide an explanation of the isomerization, but not of the color changes.

In the present work the phenylhydrazones of α-keto-γ-butyrolactone and ethyl α-keto-γ-cyanobutyrate, recovered from the reaction mixtures, were found to be isomeric with the phenylhydrazones initially used. However, the phenylhydrazone of ethyl levulinate, a small portion of which was recovered, was not isomerized.

Experimental

Typical procedures are given to illustrate the various conditions employed. Other preparations are indicated in the table.

1. Use of Boron Fluoride Etherate in Acetic Acid. (a) 3-Isopropylindole.—To 24 g. of the distilled phenylhydrazone of isovaleraldehyde[4] was added 36 cc. of glacial acetic acid and 17.5 g. of boron fluoride etherate. Reaction began when the mixture was shaken. The flask was connected to a vertical condenser and the mixture was allowed to reflux. When the spontaneous boiling ceased, refluxing was continued for fifteen minutes by external heating. The mixture was poured into 200 cc. of water (to dissolve the ammonia–boron fluoride) and the aqueous suspension was extracted with two 75-cc. portions of ether. The ether extract was washed with aqueous sodium bicarbonate and dried over anhydrous potassium carbonate. Distillation yielded 13 g. (60%) of a light yellow oil, b. p., 138–142 (6 mm.). The picrate, after three recrystallizations from ethanol, melted at 117.5° (lit.,[4] for an unanalyzed sample, 98–99°) and was analyzed.

Anal. Calcd. for $C_{17}H_{16}N_4O_7$: C, 52.58; H, 4.15. Found: C, 52.79; H, 4.29.

(b) 1,2,3,4-Tetrahydrocarbazole.—The addition of 7.55 g. of boron fluoride etherate to a solution of 10 g. of cyclohexanone phenylhydrazone in 25 cc. of glacial acetic acid caused the production of a deep red color, but no exothermic reaction occurred until the solution was warmed. At about 65° spontaneous refluxing began, accompanied by fading of the color and precipitation of ammonia–boron fluoride. Refluxing was continued for twenty minutes after the spontaneous reaction stopped. The hot solution was filtered and the solid ammonia–boron fluoride was washed with two 5-cc. portions of hot acetic acid. On cooling, the combined filtrate and washings deposited 6.94 g. of the tetrahydrocarbazole, m. p. 117.5–118°. The filtrate was heated and diluted with an equal volume of hot water; on cooling this solution deposited 1.46 g. of the product, m. p. 118°; total yield 8.4 g. (93%).

2. Use of Gaseous Boron Fluoride and a Hydrocarbon Solvent. 2-Phenylindole.—A solution of 30 g. of acetophenone phenylhydrazone in 175 cc. of dry benzene was heated to gentle reflux. Boron fluoride was passed into the solution at a rate of about two bubbles per second for one hour and at about half this rate for an additional hour. The precipitated ammonia–boron fluoride was separated by filtration and was washed with 35 cc. of hot benzene. Cooling of the combined solutions caused the crystallization of 21 g. (76%) of the crude product, m. p. 180–183°. Recrystallization from ethanol and working up of the ethanol mother liquor gave 18 g. (67.5%) of product of m. p. 187–188°.

3. Decomposition of the Phenylhydrazone–Boron Fluoride Compound without Solvent. 2-Methylindole-3-acetic Acid.—Eighteen grams of the phenylhydrazone of ethyl levulinate was heated to its melting point (102°) and 8.3 g. of boron fluoride etherate was added dropwise. The resulting mixture underwent no apparent change during fifteen minutes at 105°, but after a few minutes with the oil-bath at 127° a vigorous reaction occurred and the mass solidified. The flask containing the mixture was allowed to cool in the oil bath. The organic material was separated from the ammonia–boron fluoride by extraction with 50 cc. of boiling absolute ethanol. Cooling of the extract caused the separation of 2 g. of the phenylhydrazone of ethyl levulinate (m. p. 102°). The mother liquor was concentrated to half volume and heated for one hour with 75 cc. of 20% aqueous sodium hydroxide. About 30 cc. of the solvent was removed by distillation and the solution was acidified with hydrochloric acid. The solid collected after cooling for one hour weighed 12.5 g. (96%) and melted at 188–194°. A sample once crystallized from acetone melted at 196–197° (dec.).

Summary

Boron fluoride is an effective condensing agent in the conversion of phenylhydrazones to indole derivatives. Several experimental procedures involving the use of boron fluoride or its etherate are described.

Tautomerization of the boron fluoride complexes of phenylhydrazones and phenylazo compounds is proposed as a basis for the explanation of the transitory colors observed during the course of the indole synthesis. The conversion of stable phenylhydrazones to the labile forms, occasionally noted in unsuccessful or partly successful indole syntheses, may be accounted for on the basis of the same tautomerization.

Urbana, Illinois Received August 27, 1943

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[18] Compounds III and IV are the boron fluoride complexes of the intermediates proposed in the Robinson and Robinson mechanism of the Fischer indole synthesis [Robinson and Robinson, *J. Chem. Soc.*, **125**, 827 (1924)].