SYNTHESIS OF HETEROCYCLES BY MEANS OF PYRIDINIUM HALIDES (REVIEW)

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Cyclization processes that take place in the presence of pyridinium halides and lead to the formation of oxygen-containing and sulfur-containing heterocycles, as well as to benzoxazoles and benzothiazoles, are examined.

The high reactivity of pyridinium chloride in dealkylation reactions was first reported by Prey in 1941 [1]. Pyridinium chloride, in addition to its use as a reagent for the preparation of phenols from their alkyl ethers [2], has also been widely used for 15 yr in organic synthesis in, for example, dehydration, chlorination, and isomerization, reactions or in rearrangements and protolysis (see [3] and a series of publications by R. Royer and co-workers entitled "Reactions involving pyridinium chloride" in Bull. Soc. Chim. France from 1968 to 1975).

Very recently it was established that the properties of pyridinium bromide are equal to, if not superior, to the properties of pyridinium chloride in this respect [4-7]. The same to a lesser extent also holds for various pyridinium fluorides in some cases [8, 9].

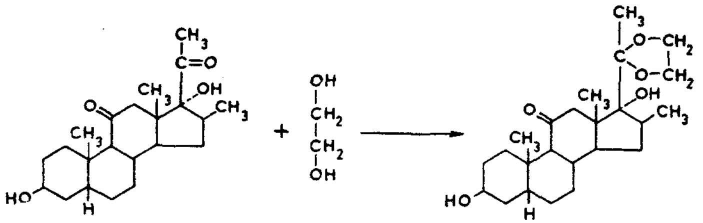
Despite the fact that the chemistry of pyridinium halides is presently only in its initial stage of development, the available data already make it possible to review some preliminary results. The problems of the synthesis of heterocycles by means of pyridinium chloride and bromide will be illuminated in the present paper.

At the foundation of these syntheses lie both intramolecular or intermolecular cyclohydration reactions and some other methods of heterocyclization.

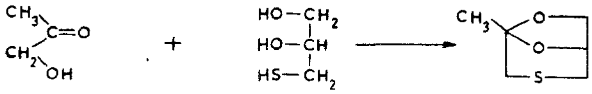
1. CYCLODEHYDRATION

1.1. Intermolecular Cyclodehydration

In 1966 it was established that the condensation of ethylene glycol with 13α,17α-dihydroxy-16β-methylpregnane-11,20-dione proceeds in higher yield (100%) in the presence of pyridinium chloride than in the presence of the classical catalyst for the formation of acetals, p-toluenesulfonic acid [10]:



1-Methyl-2,8-dioxa-6-thiabicyclo[3.2.1]octane was synthesized in 90% yield in 1971 by means of pyridinium chloride generated in situ [11]:



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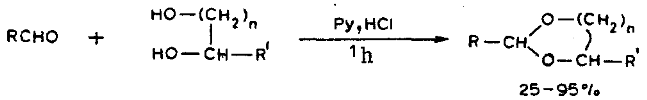
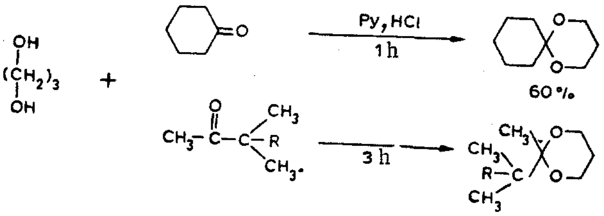
However, only a systematic study made it possible to recommend this reagent as a general one in the synthesis of 1,3-dioxanes and 1,3-dioxolanes from aliphatic, aromatic, and heterocyclic aldehydes, as well as from ketones, including alicyclic or sterically hindered ketones [12]:

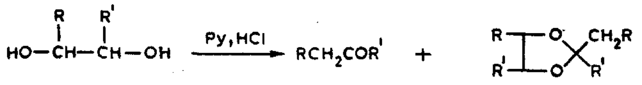


Py - here and subsequently, pyridine ; R = alkyl, aryl, hetaryl
R' = H, CH_3 ; n = 1,2



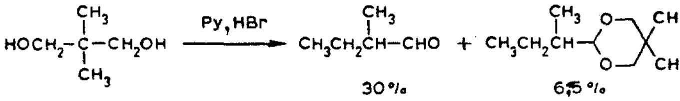
R = H (30%), CH_3 (10%)

Condensation to a heterocycle with two oxygen atoms between diols, aldehydes, or ketones formed from them as a result of pinacol rearrangement proceeds in the same way under the influence of pyridinium chloride [13]:



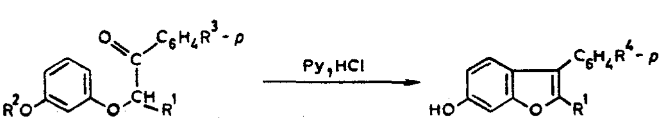
R = R' = H	15%	20%
R = CH_3, R' = H	5%	49%
R = R' = CH_3	70%	20%

Although this reaction sometimes does not occur in the presence of pyridinium chloride, it can be realized by means of pyridinium bromide:



1.2. Intramolecular Cyclodehydration

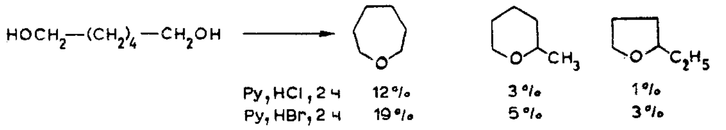
1.2.1. Cyclodehydration with the Participation of an Enolizable α-Ketomethylene Group. Aryloxyacetophenones and α-aryloxypropiophenones form 3-arylbenzofurans, which are obtained in 40-60% yields, depending on the heating time and the structure of the starting compound.



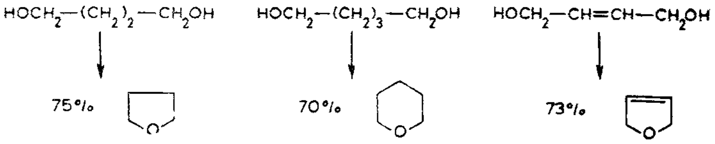
R^1, R^2 = H, CH_3 ; R^3 = H, OCH_3 ; R^4 = H, OH

Although other dehydrating agents such as sulfuric acid, phosphorus oxychloride, or polyphosphoric acid (PPA) also make it possible to effect transformations of this type, the advantage of pyridinium chloride consists in the fact that demethylation occurs simultaneously when it is present, and it thus becomes possible to accomplish the one-step synthesis of hydroxy-substituted arylbenzofurans [14, 35].

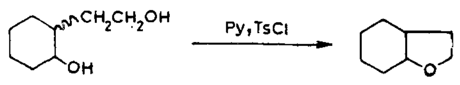
1.2.2. Cyclodehydration Involving Two Hydroxyl Groups in the Starting Compound. Oxygen-containing heterocycles are formed by intramolecular cyclodehydration in the course of various reactions of pyridinium halides with diols. They may be side products, as in the case of diethylene glycol, which forms more linear polymers than dioxane (in 30% yield in the presence of pyridinium chloride) [2] or 1,6-hexanediol, the corresponding oxonium derivative of which, through an intermediate carbonium ion, forms more unsaturated derivatives than heterocyclic compounds [7, 13]:



Heterocycles may become the chief dehydration products if the structure of the diols promotes this, as in the case of 1,4-butanediol, 1,5-pentanediol, or 2-butene-1,4-diol [13]:

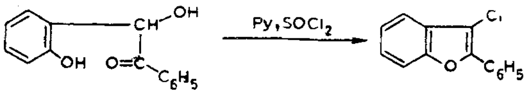


Cyclodehydration of this sort may also be accomplished in the alicyclic series by means of a mixture of toluenesulfonyl chloride and pyridine [16]:

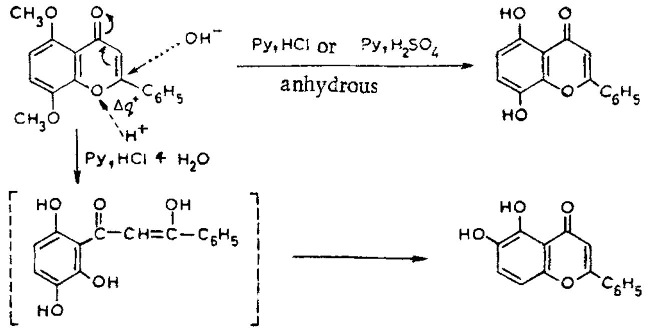


Cyclodehydration of this type occurs with the participation of the phenolic hydroxyl group and the enolic hydroxyl group of a substituent in the ortho position.

The reaction of 2-hydroxybenzene with thionyl chloride in pyridine [17] proceeds in this way with subsequent chlorination:



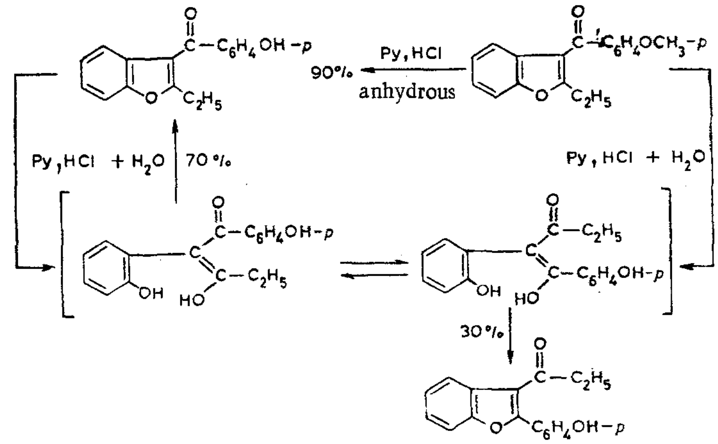
This is also observed in the rearrangement of some oxygen-containing heterocycles, the ring of which is capable of opening as a result of nucleophilic reaction under the influence of more or less hydrated pyridinium chloride. The same also occurs in the demethylation of 5,8-dimethoxyflavone, which is accompanied by isomerization to 5,6-dihydroxyflavone if the reaction occurs in the presence of water, whereas only 5,8-dihydroxyflavone is formed as a result of heating at 200° for 6 h in completely anhydrous pyridinium chloride or sulfate [18]:



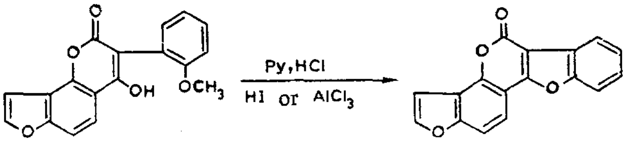
The partial isomerization of 2-ethyl-3-(4-hydroxybenzoyl)benzofuran to 2-(4-hydroxyphenyl)-3-propionylbenzofuran, which promotes the demethylation of 2-ethyl-3-(4-methoxybenzoyl) benzofuran [19], proceeds similarly (see the top of the following page).

Thus only "pseudoaromatic" heterocyclic systems, particularly chromones or benzofurans with an electron-acceptor grouping in the 3 position, undergo rearrangement [20, 21]. Rearrangement was not observed in the demethylation of 2-ethyl-3-(4-methoxybenzoyl)benzo[b]-thiophene.

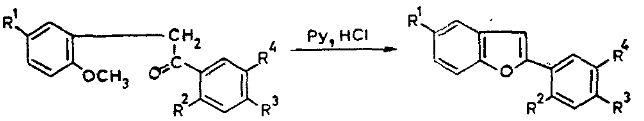
1.2.3. Cyclodehydration with the Participation of the Phenolic or Enolic Hydroxyl Group of the Starting Compound and the Hydroxyl Group Formed as a Result of Dealkylation. Some of these double transformations in which a free phenolic hydroxyl group participates, as, for



example, the cyclization of 3-(2-methoxyphenyl)-4-hydroxyfuro[2,3-h]coumarin, may be realized equally successfully by means of hydriodic acid or aluminum chloride and by means of pyridinium chloride [22]:

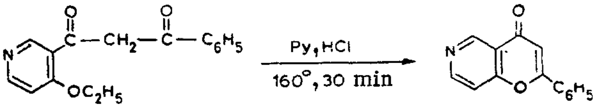


On the other hand those transformations in which an enolizable α-ketomethylene chain participates are realized only in the presence of more effectively acting pyridinium halides. The use of the latter made it possible to obtain substituted 2-arylbenzofurans (particularly the nitro and hydroxy derivatives) in high yields from 2-methoxydesoxybenzoins [23, 24]:



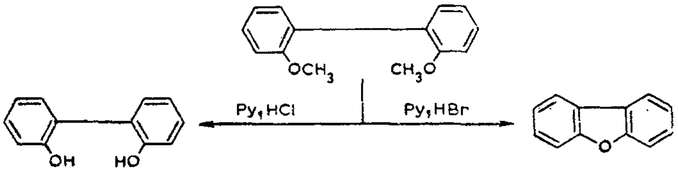
$R^1, R^4 = H, NO_2$; $R^3 = H$; $R^2 = OCH_3$ ($\longrightarrow$ OH)
$R^1, R^2, R^4 = H$; $R^3 = H, OCH_3$ ($\longrightarrow$ OH)

The same method was used in the synthesis of 6-azaflavone (in 75% yield), which could not be obtained by a different method [25]:

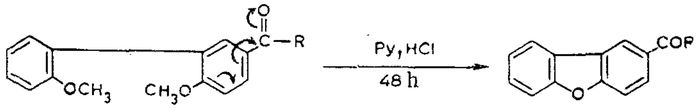


1.2.4. Cyclodehydration with the Participation of Two Hydroxyl Groups Formed as a Result of Demethylation. These reactions have already found wide application in the synthesis of dibenzofurans, xanthones, and phenoxazines.

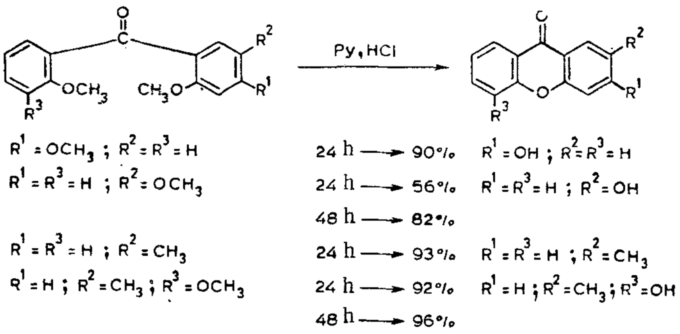
2,2'-Dimethoxydiphenyl is converted quantitatively to dibenzofuran by heating for 48 h in excess pyridinium bromide. Under the same conditions pyridinium chloride brings about only demethylation without appreciable cyclodehydration [26]:



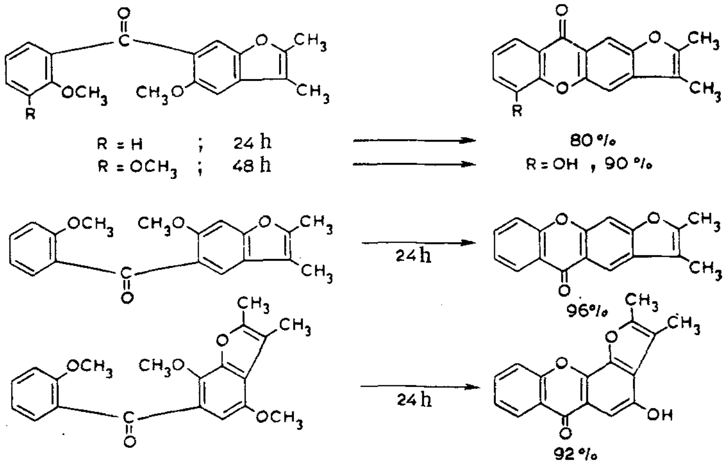
Cyclodehydration can, nevertheless, be accomplished in 40-60% yields by means of pyridinium chloride if the reaction is continued for a longer time or is facilitated by the introduction of an electron-acceptor substituent in the necessary position [27]:



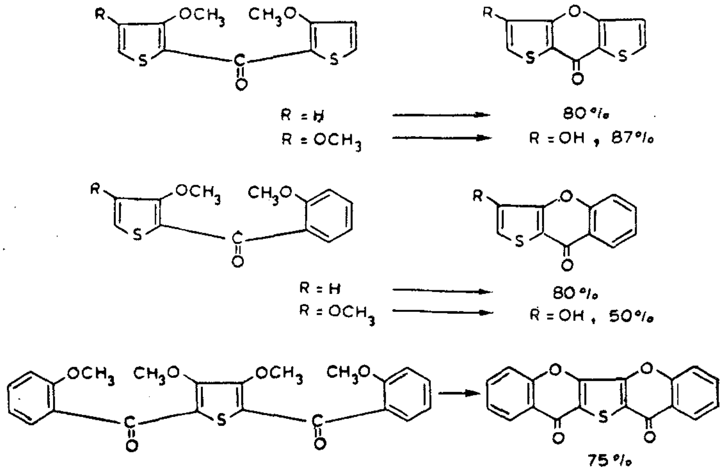
In the same way, the yield of the product of "xanthonization" of 2,2'-dimethoxybenzophenones by means of pyridinium chloride, which does not exceed 30% after heating for 4 h [28], becomes satisfactory after heating for 24 or 48 h [29]:



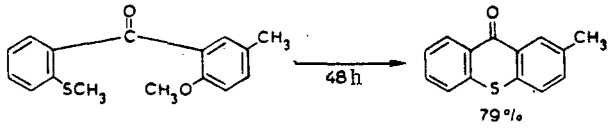
This method can be used for the synthesis of furoxanthones, particularly hydroxy-substituted furoxanthones, in yields of the same order [29]:



The method was relatively successfully used for the preparation of sulfur isologs of xanthones from 2-(2-methoxybenzoyl)-3-methoxythiophene, 2-(3-methoxy-2-thenoyl)-3-methoxythiophenes, and even from 2,5-bis(2-methoxybenzoyl)-3,4-dimethoxythiophenes [30, 31]:

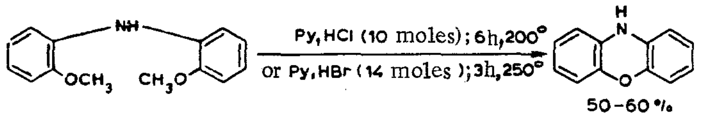


Cyclodehydration of the same type may also occur through the hydroxyl and sulfhydryl groups formed in situ in the demethylation of 2-methoxy-2'-methylthiobenzophenones, exceptionally under the influence of pyridinium chloride [29]:

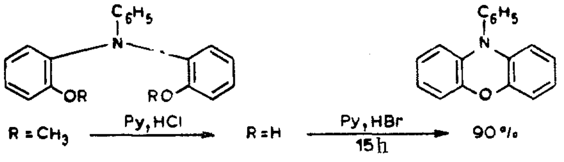


The fact that primarily thioxanthone and only traces of xanthone are formed as a result of this reaction is explained by the fact that since the oxygen atom is more electronegative than the sulfur atom, the resulting hydroxyl group is protonated more readily than the benzyhydryl group. The first of these groupings is eliminated more rapidly than the second during acid attack on the intermediate product of demethylation.

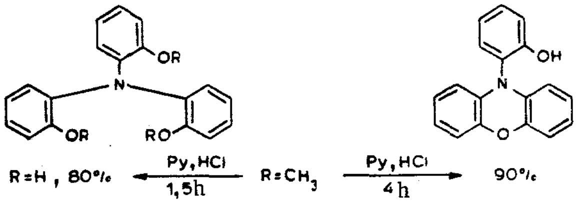
Phenoxazines can be synthesized by reaction of 2,2'-dimethoxydiphenylamines with pyridinium halides. Little heed should be paid to the first research in which pyridinium chloride was used, since the reaction was carried out with a very small amount of N-acetyl-2,2',5-trimethoxy-6-methyldiphenylamine, and the hydroxyphenoxazine was oxidized to the quinoneimine [32]. The preparation of phenoxazine itself from 2,2'-dimethoxydiphenylamine also proved to be unprofitable, since large amounts of pyridinium halide were necessary for this [5]:



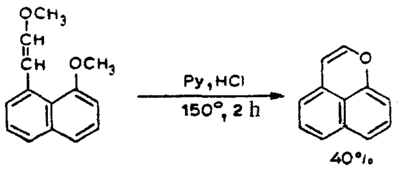
Pyridinium chloride does not make it possible to effect the cyclization of N-phenyl-2,2'-dimethoxydiphenylamine, from which only the corresponding diphenol is formed. The latter undergoes cyclodehydration only with pyridinium bromide, which is more "acidic" and makes it possible to work at higher temperatures [5]:



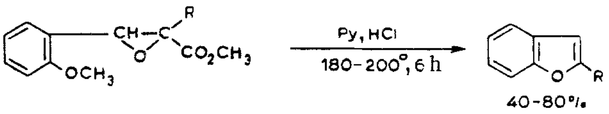
However, pyridinium chloride is capable of converting 2,2',2"-trimethoxytriphenylamine to N-(2-hydroxyphenyl)phenoxazine if the heating time is sufficient to decompose the extremely stable and isolable [33] equimolecular addition product, which is formed initially with the corresponding triphenol [5]:



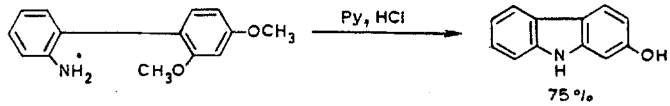
Another example of this method for the direct preparation of an oxygen-containing heterocycle from a dimethoxy derivative is the recently described synthesis of 1-oxaphenalene [34]:



Finally, we should point out the preparation of 2-alkyl- or 2-arylbenzofurans from 2-methoxyarylglycidic esters, in which two hydroxyl groups formed as a result of demethylation and cleavage of the epoxide bond also participate [35]. The simultaneous elimination of an ester grouping by the protolytic and decarboxylating action of pyridinium halide has become the subject of independent detailed research [36-38]:

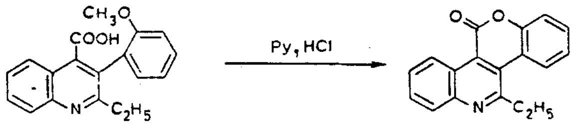


1.2.5. Cyclodehydration with the Participation of Amino and Hydroxyl Groups Formed as a Result of Demethylation. The only presently known example of cyclodehydration of this type is the formation of 2-hydroxycarbazole from 2-amino-2',4'-dimethoxydiphenyl under the influence of pyridinium chloride; hydrobromic acid in this case gives rise only to demethylation [39]:

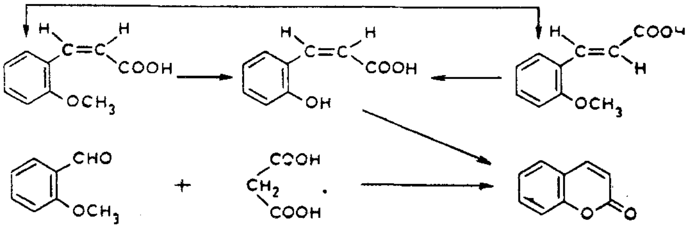


The heterocyclization of aromatic compounds through previously existing or newly formed hydroxyl groups in the ortho position of an iminocarbonium group or the corresponding acetamido group is the most typical reaction and has been widely used, as we will demonstrate somewhat later.

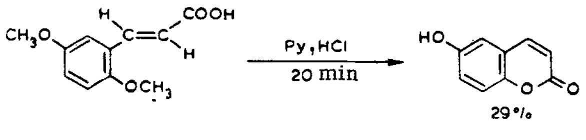
1.2.6. Cyclodehydration with the Participation of Carboxyl and Hydroxyl Groups Formed as a Result of Demethylation. Although this "coumarinization" process has been observed for 2-ethyl-3-(2-methoxyphenyl)cinchoninic acid [40], it has been used primarily for the cyclization of methoxycinnamic acids.



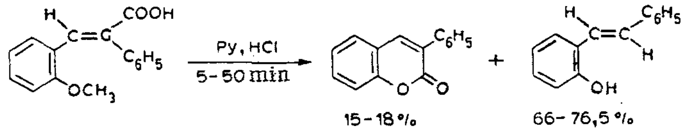
It has been established that pyridinium chloride, at the boiling point of the reaction mixture, promotes the partial isomerization of cis-methoxycinnamic acid to the trans isomer and that both acids subsequently form cis-hydroxycinnamic acid, which undergoes cyclization to coumarin [41]:



This double demethylation-cyclodehydration reaction is somewhat hindered by side decarboxylation, and the yield of coumarin after heating for 30 min does not exceed 55% from cis-methoxycinnamic acid and 47% from the trans isomer. The yield of cyclization product is even lower when the reaction is complicated by secondary demethylation:

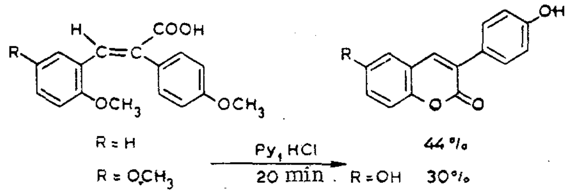


Considerable amounts of coumarin can be obtained directly from malonic acid and o-anisaldehyde, the condensation of which to methoxycinnamic acid is accomplished in situ in the presence of pyridinium chloride. In order to avoid dilution of the reaction medium, it is necessary to remove the acetic acid formed during the reaction [41]. Under the same conditions, 2-methoxy-α-phenyl-trans-cinnamic acid (of the cis-stilbene type [42]) forms primarily trans-stilbene rather than 3-phenylcoumarin [41, 43]:



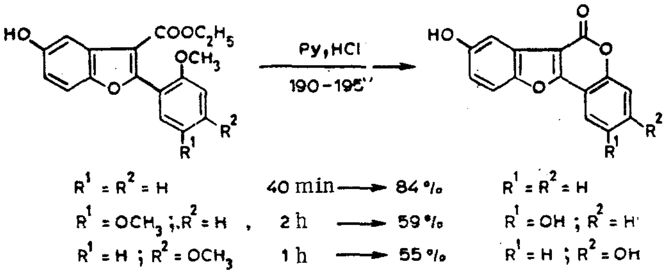
The fact that 2-methoxy-α-phenyl-trans-cinnamic acid gives a coumarin in lower yield than 2-methoxy-trans-cinnamic acid is undoubtedly a consequence of the fact that the phenyl group in the α position relative to the carboxyl group hinders the conversion of the trans isomer to the cis isomer, which is capable of undergoing cyclodehydration.

Some polymethoxy derivatives of α-phenylcinnamic acid such as 2-methoxy- and 2,5-dimethoxy-α-(4-methoxyphenyl)cinnamic acid form more coumarin than 2-methoxy-α-phenylcinnamic acid [41]:



Under the influence of pyridinium chloride, 2,4-dimethoxy-α-phenylcinnamic acid undergoes resinification and gives 3-phenyl-6-hydroxycoumarin in no higher than 10% yield.

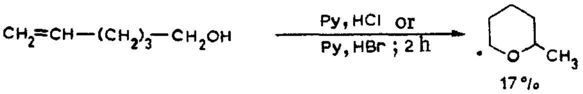
The synthesis of benzofuro[3,2-c]benzopyranones is a recent example of lactonization under the influence of pyridinium chloride, which very rapidly converts the methoxy and carbethoxy groups, respectively, to hydroxyl and carboxyl groups [44]:



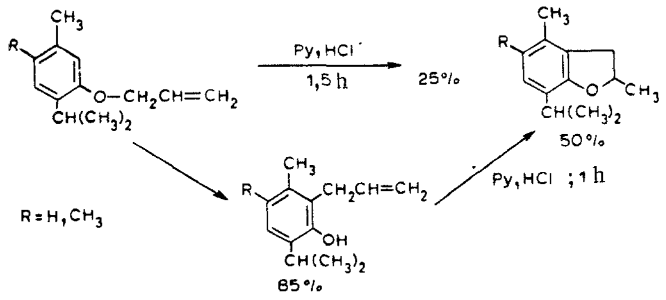
2. HETEROCYCLIZATION

2.1. Heterocyclization with the Participation of a Hydroxyl Group and an Ethylene Bond

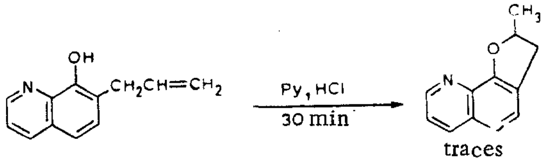
2-Methyltetrahydropyran is formed by heating hex-5-en-1-ol in the presence of pyridinium bromide or chloride [7] or 85% phosphoric acid (PPA) [45] as a result of attack by the oxygen atom on the double bond:



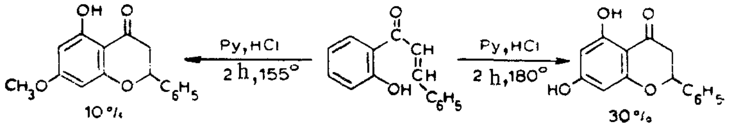
Coumarins are formed via the same mechanism from allyl-substituted thymol or 4-methylthymol, as well as from allyl ethers, which undergo rearrangement to these allyl-substituted derivatives [46]:



However, in contrast to sulfuric acid, pyridinium chloride is less suitable for the cyclization of 7-allyl-8-hydroxyquinoline [47]:

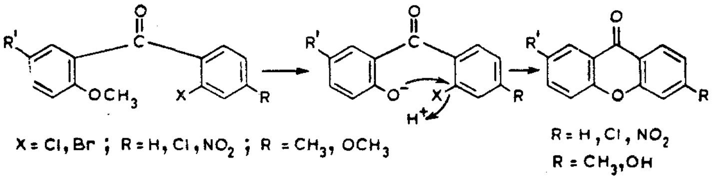


Depending on the temperature, 4,6-dimethoxychalcone undergoes cyclization with partial demethylation to 2,3-dihydrotectochrysin or with complete demethylation to 2,3-dihydrochrysin [48]:

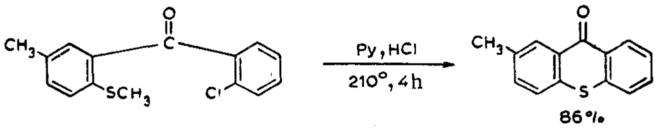


2.2. Heterocyclization with the Elimination of a Hydrohalic Acid

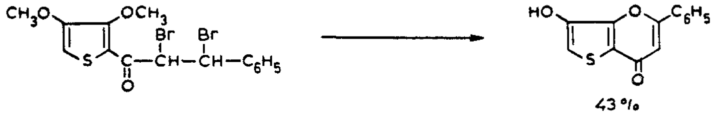
When 2-halo-2-methoxybenzophenones are heated to 210° for 30 min or 1 h in a fourfold excess of pyridinium chloride, they form only the corresponding hydroxy derivatives, whereas an increase in the heating time to 6-48 h leads to their heterocyclization to xanthones in 45-97% yields [49]:

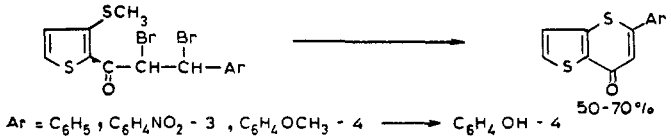


Considering the mechanism of the reaction, it is not surprising that 2-chloro-2'-methylthiobenzophenones undergo "thioxanthonization" more rapidly than 2-methoxy-2'-methylthiobenzophenones or 2-chloro-2'-methoxybenzophenones undergo "xanthonization" [49].



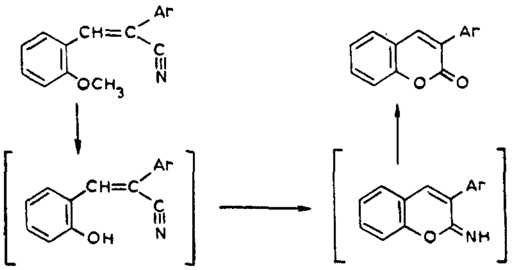
Various thiophene isologs of flavone and thiaflavone have been similarly obtained. This method consists in demethylation and subsequent heterocyclization, as a result of which hydrogen halide is split out [30, 31]:





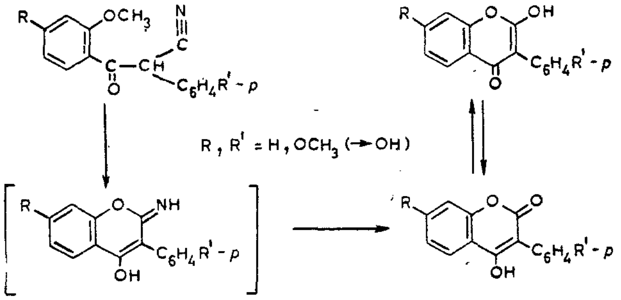
2.3. Heterocyclization with the Participation of Cyano and Hydroxyl Groups Formed as a Result of Demethylation

When 3-(2-methoxyphenyl)-2-arylacrylonitriles are refluxed in excess pyridinium chloride, they are rapidly converted to iminocoumarins, which immediately form coumarins when they are subjected to reaction with water [50]:



This method has been widely used for the preparation not only of 3-arylcoumarins but also of 3,4-diarylcoumarins and furocoumarins, as well as their hydroxyl derivatives [51-57].

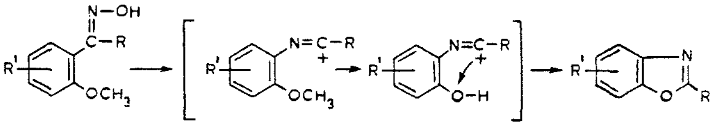
The reaction has also found application in the synthesis of isoflavonols, particularly hydroxy-substituted derivatives [36]:



2-Methoxy-α-cyanodesoxybenzoins also behave similarly under the influence of hydrobromic acid, which, however, gives rise to a side reaction of partial decyanation; this in turn lowers the yield of the heterocyclization product [58]. Heterocyclization may also be accomplished by means of aluminum chloride, which does not cause simultaneous demethylation of the other methoxy group in the ortho position with respect to the carbonyl group. Another form of heterocyclization in which the cyano group participates is the conversion of methyl-2-cyanobenzoate to phthalimide; this transformation proceeds equally rapidly with pyridinium chloride and acids or dilute alkalis [38].

2.4. Heterocyclization with the Participation of an Intermediate Iminocarbonium Ion and a Hydroxyl Group Formed during Demethylation

Since pyridinium chloride may give rise to both Beckmann rearrangement of ketoximes [59] and dealkylation of methoxy derivatives, it is not surprising that it converts oximes of alkyl 2-methoxyaryl ketones to benzoxazoles [60]:



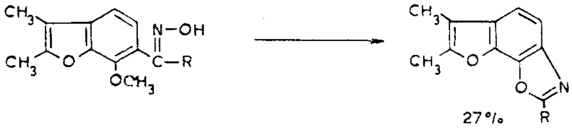
This mechanism can be confirmed by various methods (for example, by decreasing the rate of the reaction as the hydration of the pyridinium chloride is increased). In this case one can isolate methoxy- and hydroxy-substituted acetamides, which are the products of stabilization of the intermediate ions, and the corresponding amines, if the excess amount of water is not too great (about 10%); if too much water is present, the starting oxime undergoes hydrolysis to the ketone with or without subsequent demethylation.

This new method for the preparation of benzoxazoles is based on the use of readily accessible starting materials, is quite convenient, and gives the benzoxazoles in relatively high yields (about 55%); it may therefore successfully compete with most of the other methods for the preparation of benzoxazoles that have been previously employed.

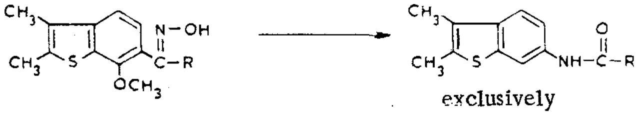
A study of the reaction of o-methoxy-substituted oximes of the benzofuran or benzo[b]thiophene series showed that the spatial orientation of the two functional groups that participate in the cyclization determines to a considerable extent the relative amount of benzoxazole obtained through the acetamide, which is primarily formed in this reaction [60, 62]:

Preferred spatial orientation

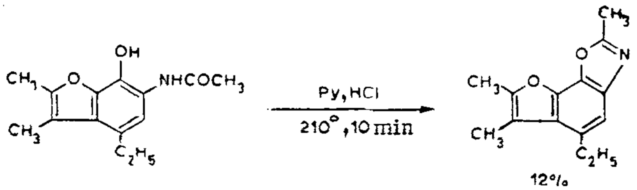
Less preferred spatial orientation



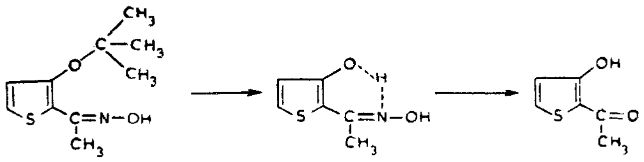
Unfavorable spatial orientation



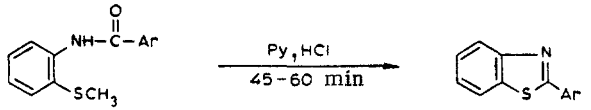
It follows from this that some o-hydroxy-substituted acetamides are capable of giving benzoxazoles when they are treated with pyridinium chloride. An example of this is 2,3-dimethyl-4-ethyl-6-acetamido-7-hydroxybenzofuran, which is resistant to the action of high temperatures and prolonged refluxing with hydrochloric acid but rapidly forms a considerable amount of 2,6,7-trimethyl-5-ethylfuro[2',3':1,2]benzo[5,6]oxazole in the presence of pyridinium chloride [63]:



A benzoxazole is not formed in the case of 2-acetyl-3-tert-butoxythiophene, which on treatment with pyridinium chloride splits out a tert-butyl group and is converted to the acetyl derivative without undergoing the rearrangement necessary for cyclization under any conditions whatsoever. This is a consequence of stabilization due to the formation of a chelate with the hydroxyl group which, in all likelihood, is formed more rapidly from the tert-butoxy derivative than from the methoxy derivative [30, 64]:

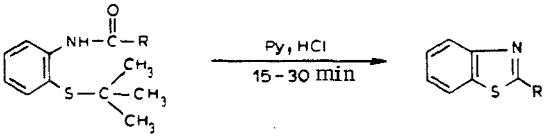


A similar process has been used in the synthesis of benzothiazoles. When many 2-methylthioaroylanilides are heated in pyridinium chloride, they form considerable amounts [according to gas–liquid chromatography (GLC)] of 2-arylbenzothiazoles, although their preparative isolation is difficult in a number of cases [65]:



		Found, %	Calc. %
Ar = C_6H_5		70	35
$C_6H_3Cl_2$ - 2,4		75	56
$C_6H_4OCH_3$ - 2	→ C_6H_4OH - 2	50	29
$C_6H_4OCH_3$ - 4	→ C_6H_4OH - 4	traces	0
2-thienyl		70	30
5-chloro-2-thienyl		50	2

The use of o-tert-butylthio-substituted anilides makes it possible to considerably increase the rate of formation and raise the yields of cyclization products [65]:



R = CH_3		75%
C_6H_5		82%
$C_6H_4OCH_3$ - 4	→ C_6H_4OH - 4	72%

The data presented in this paper illustrate well the effectiveness of pyridinium halides as heterocyclization agents. Their action can be easily modified and adapted to each case by simple modification of the reaction conditions. Inasmuch as they are more convenient to use than hydrohalic acids, they can almost always be substituted for them and frequently may supersede them.

The pyridinium halides prove to be even more useful as carriers of hydrohalic acids that are inconvenient for work in anhydrous media and at relatively low temperatures. In addition, since some of their properties differ from those of hydrohalic acids, the pyridinium halides can be used as specific reagents, the research on which is worthy of future correlation.

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SYNTHESIS AND PROPERTIES OF HETEROCYCLIC CARBONIUM SYSTEMS.

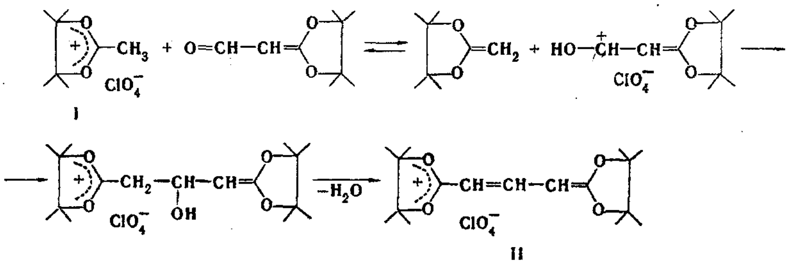
V.* SYNTHESIS AND REACTIONS OF SOME CYANINES BASED ON DIOXOLANIUM SALTS

L. V. Mezheritskaya, E. S. Matskovskaya,
and G. N. Dorofeenko

UDC 547.729.7.07

Bis(4,4,5,5-tetramethyl-2-dioxolano)trimethylidynecyanine was synthesized by condensation of 2-methyl-1,3-dioxolanium perchlorate with 2-formylmethylene-1,3-dioxolane by heating (90-100°C) in acetic anhydride. It is shown that the 1,3-dioxolane also condenses under similar conditions with pyrylium salts containing active methylene and methyl groups to give unsymmetrical dioxolanopyrylocyanines. The synthesized cyanines react with $HClO_4$ to give unstable diperchlorates, which readily lose a molecule of $HClO_4$ to give the starting cyanines. Concentrated HCl decomposes one of the dioxolane rings of the symmetrical cyanine, and refluxing with dilute HCl brings about its destruction to low-molecular-weight unidentified compounds. The unsymmetrical cyanine from the pyrylium salt is resistant to the action of acids but is hydrolyzed by alkalis with cleavage of the pyrylium ring to a diketone. The action of Br_2 on the dioxolanocyanine leads to the addition of bromine to the double bonds and replacement of the ClO_4^- ion by Br^-.

Until now, cyanine dyes that contain a dioxolanium cation were unknown. Our attempt to synthesize a dioxolanocyanine by the traditional method from 2-methyl-1,3-dioxolanium perchlorate (I) and ethyl orthoformate led only to a 2-(β-ethoxyvinyl)-1,3-dioxolanium salt [2], which does not undergo further reaction with starting I. An increase in the temperature and the heating time leads to decomposition of the extremely labile dioxolanium cation. We were able to synthesize dioxolanocyanine II only by condensation of I with 2-formylmethylene-1,3-dioxolane obtained from the 2-(β-ethoxy)vinyl derivative by the action of alkali [2]. The reaction proceeds when the components are heated moderately (90-100°C) in acetic anhydride until they dissolve completely.



Under similar conditions, 2-formylmethylene-1,3-dioxolane also condenses with pyrylium salts containing active methyl or methylene groups to give unsymmetrical dioxolanopyrylocyanines (Table 1). 2-Methyl-4,6-diphenylpyrylium perchlorate and pyridinium, quinolinium, and

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*See [1] for communication IV.

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