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RADICAL ADDITION OF ORGANIC HALIDES TO MULTIPLE BONDS IN THE SYNTHESIS OF HETEROCYCLIC COMPOUNDS. (REVIEW)

K. I. Kobrakov[1] and A. V. Ivanov[2]

The addition of polyhalides to multiple bonds in the synthesis of various heterocyclic compounds is discussed.

Keywords: benzoxazines, halopyridines, pyrans, furans, Kharasch reaction.

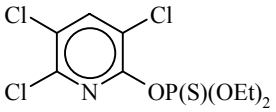
The radical addition of organic halides to double bonds (Kharasch addition) is a well developed tool of organic synthesis. The advantages of the method include the simplicity of the apparatus, the ready availability of the starting compounds, the possibility of varying them over a wide range, and the production of highly functionalized compounds that are difficult to obtain by other methods.

The present review is devoted to the application of the Kharasch reaction to the synthesis of various nitrogen- and oxygen-containing heterocyclic compounds – polychloropyridines, pyrans, and tetrahydrofurans. It does not deal with aspects of the synthesis of azoles and furans based on the products from the addition of polyhalides to methyl vinyl ketone and vinyl butyl ether, which were examined in [1-4].

1. NITROGEN-CONTAINING RINGS

1.1. Production of Polyhalogenated Pyridines

Compounds containing a halogenated pyridine ring are of great interest as insecticides, fungicides, and herbicides. As examples it is possible to cite such products as Dursban (**1**) [5], Alphacor (**2**) [6], Topic (**3**) [7], CGA 143268 (**4**) [8].



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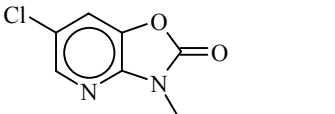

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[1] A. N. Kosygin Moscow State Textile University, Moscow, Russia; e-mail: office@nesta.ac.ru.
[2] Institute of Physiologically Active Substances, Russian Academy of Sciences, Moscow, Russia. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 579-591, May, 2001. Original article submitted September 15, 2000.

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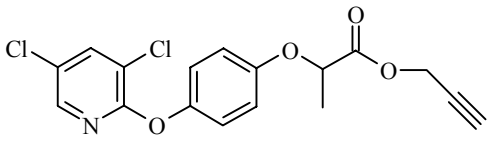

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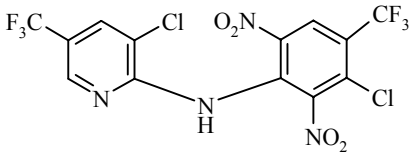

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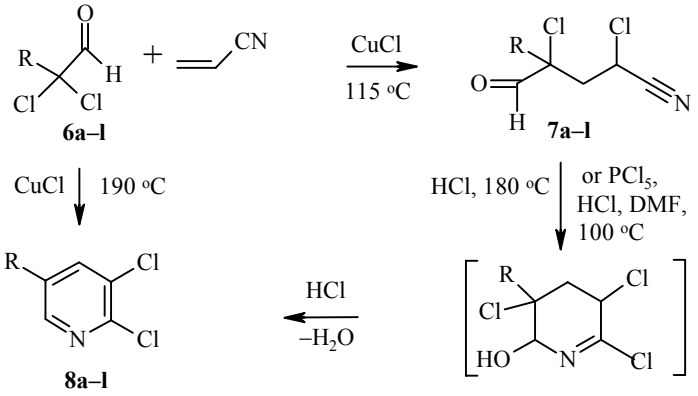
One method for the production of polyhalogenated pyridines is the addition of α-halogenated aldehydes to α,β-unsaturated nitriles [9-11]. The synthesis can be carried out with isolation of the intermediate adducts (1:1) followed by cyclization or in a single stage:



The yields of the pyridines in the reaction of various aldehydes with acetonitrile are given in Table 1.

TABLE 1. The Transformation of 2,2-Dichloro Aldehydes $RCCl_2CHO$ into Pyridines (in the Presence of 6 mole % of CuCl in Acetonitrile for 30 min) [9]

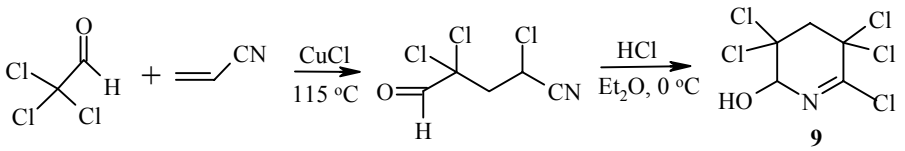
Compound	R	mp/bp	Yield, %
8a	Cl	49-51°C	65
8b	CH_3	46-47°C	53
8c	CF_3	80°C/20 mm Hg	60
8d	CH_2–CH_3	72°C/0.1 mm Hg	49
8e	CH_2–CH_2Cl	97°C/ 0.1 mm Hg	57
8f	CH_2–$CHCl_2$	89-90°C	50
8g	CH_2–CCl_3	90°C	46
8h	*n*-C_3H_7	78°C/0.01 mm Hg	35
8j	*n*-C_3H_7	54°C/0.06 mm Hg	33
8k	*n*-C_4H_9	84°C/0.2 mm Hg	52
8l	*n*-C_5H_{11}	105°C/0.06 mm Hg	51

The most active catalysts in the addition of α-chloro aldehydes to unsaturated nitriles are copper and its salts. The effect of the type of catalyst on the yield of 2,3,5-trichloropyridine in its single-stage production by the reaction of chloral with acrylonitrile can be represented in the following way [9]:

Catalyst	Cu	CuCl	$RuCl_2(Ph_3P)_3$	$NiCl_2$	$FeCl_2$	$ZnCl_2$	$MnCl_2$
Yield, %	57	65	44	2	2	10	6

If trichloromethyl ketones are used in the reaction with acetonitrile, it is possible to synthesize 6-substituted 2,3,5-trichloropyridines [11].

Ring closure without aromatization is also possible. Thus, 2,3,5,5-tetrachloro-6-hydroxy-3,4,5,6-tetrahydropyridine (**9**) is formed during treatment of the adduct of chloral and acetonitrile with anhydrous hydrogen chloride in diethyl ether at 0°C [12]:



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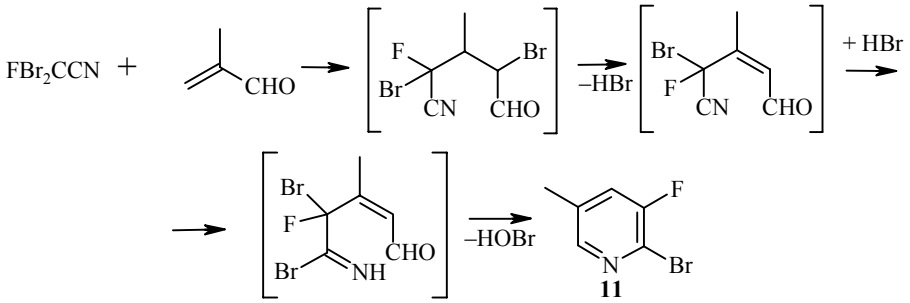
An alternative method for the synthesis of chlorinated pyridines is the addition of α-halogenonitriles to α,β-unsaturated carbonyl compounds (which takes place under milder conditions), followed by cyclization of the adducts that form [13-19]. The adduct can undergo cyclization during attempts at purification. Thus, in the case of the addition of dibromoacetonitrile to methacrolein the initially formed linear adduct can only be detected by spectroscopy [14]. It is possible that the cyclization is catalyzed effectively by the hydrogen bromide released from the adduct, but the mechanism of this process remains largely unclear.



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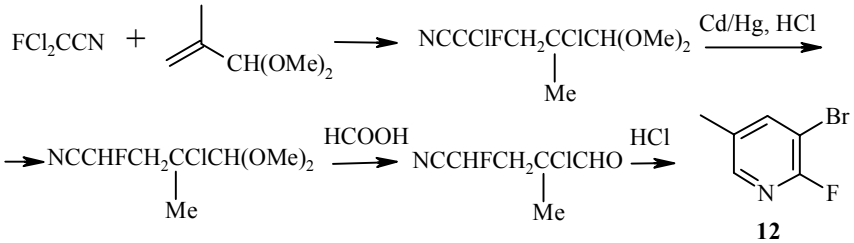
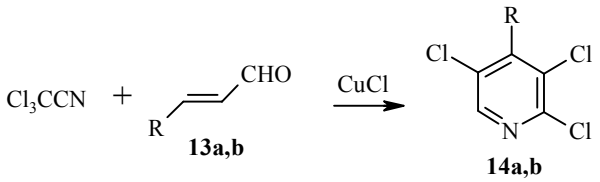
In rare individual cases it is impossible to close the pyridine ring. This is due to the specific structure of the adducts. In particular, it was not possible to obtain a heterocycle from the product from the addition of dichlorofluoroacetonitrile to methacrolein. This is explained by the absence of a hydrogen atom at the α position to the nitrile group. It was possible to obtain the expected 2-chloro-3-fluoro-5-methylpyridine (**12**) as a result of the following chain of transformations:



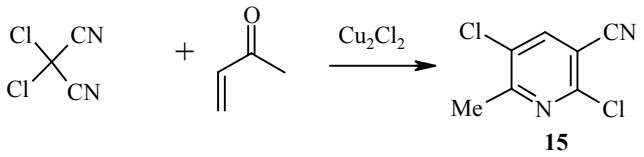
12

In reaction with halonitriles it is possible to use aldehydes not only with a terminal double bond but also with an internal double bond. On account of the higher reaction temperature in this case the linear addition products were not isolated – they underwent cyclization to the corresponding pyridines substituted at position 4 [15]:

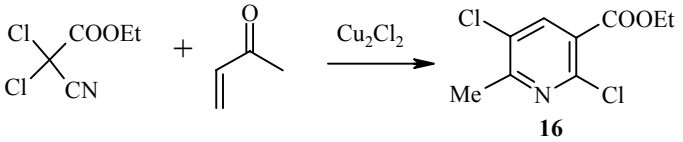


14 a R = Ph, **b** R = Me

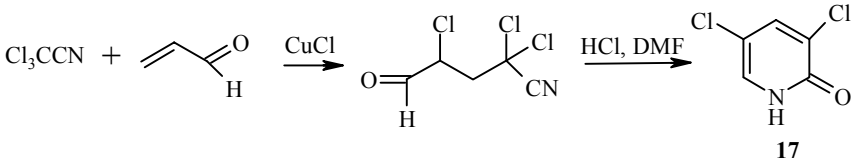
Pyridines containing a substituent at position 6 can be obtained by the addition of halonitriles to vinyl ketones [16]. When dichloromalononitrile was used in this addition reaction, cyclization led to the nitriles of the corresponding nicotinic acids, such as compound **15** [18]:



Nicotinic esters are formed in this reaction if dichlorocyanoacetic acid is used [19]:

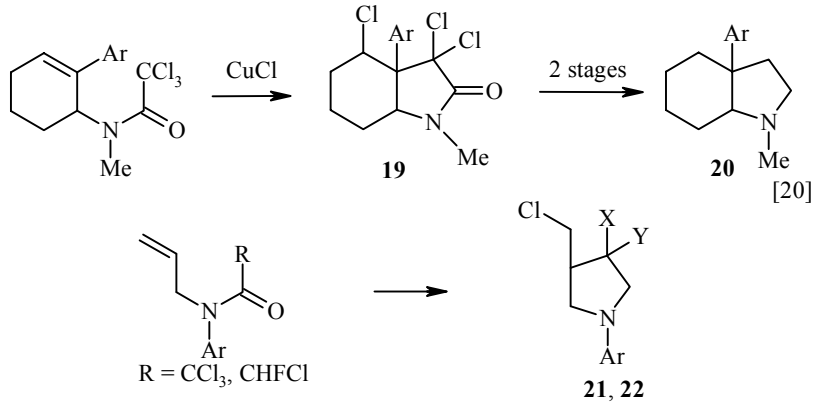


As a result of ring closure it is possible to obtain not only pyridines but also 2-pyridones. For the synthesis of pyridones the cyclization of the linear adducts is conducted with hydrogen chloride in organic solvents [15, 16]. For example, 3,5-dichloro-2-pyridone is formed if trichloroacetonitrile and acrolein are used.



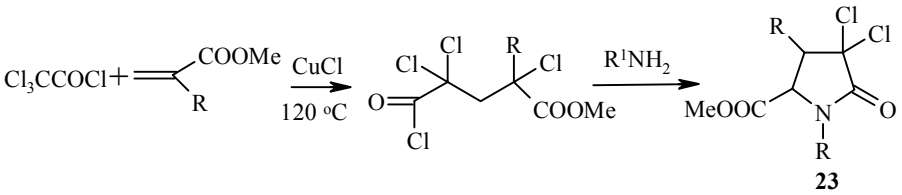
1.2. Other Nitrogen-containing Systems

Examples of the closure of a pyrrolidine ring by intramolecular addition of a polyhalomethyl group to a double bond are known:



21 X = Y = Cl, **22** X = H, Y = F [21, 22]

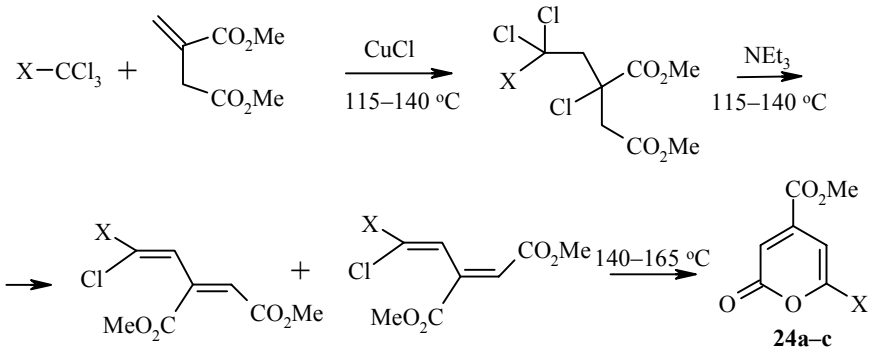
Another method for the synthesis of N-substituted chlorinated pyrrolidones involves addition of the chlorides of α-chloro carboxylic acids to alkenes and further treatment of the obtained adduct with amines [9]:



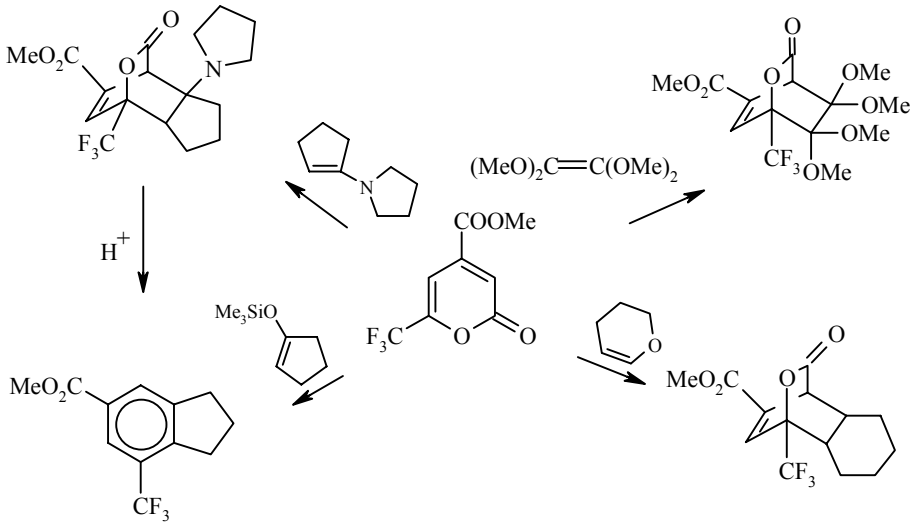
2. OXYGEN-CONTAINING RINGS

2.1. Pyran Ring

The addition of polyhalogenated organic compounds to dimethyl itaconate leads to useful starting compounds for the synthesis of polyfunctionalized α-pyrones [9]. The method for their production and some further transformations are represented in the following schemes:

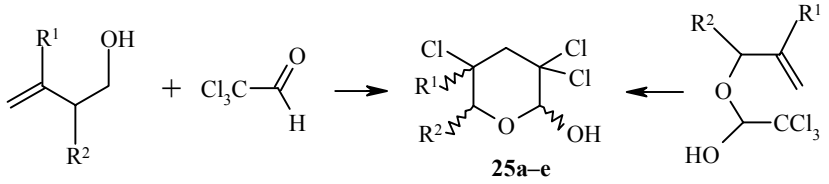


24 a X = Cl, **b** X = COOEt, **c** X = CF_3



Appreciable amounts of tetrahydropyran rings are formed in addition to the main products from the cyclization of allyl trichloroacetates [23] (see the next section). In our opinion the change in the direction of the reaction may be due to change in the character of cleavage of the C–Cl bond depending on the catalyst employed. If large amounts of the compounds of metals (such as copper monochloride) that enter readily into single-electron transfer are used, the main reaction becomes homolytic cleavage of the C–Cl bond, leading to radical closure of the five-membered ring. In another case with the formation of a complex with a catalyst having the characteristics of Lewis acids a positive charge can remain on the carbon atom, leading to the formation of a pyran ring as a result of electrophilic addition to the double bond.

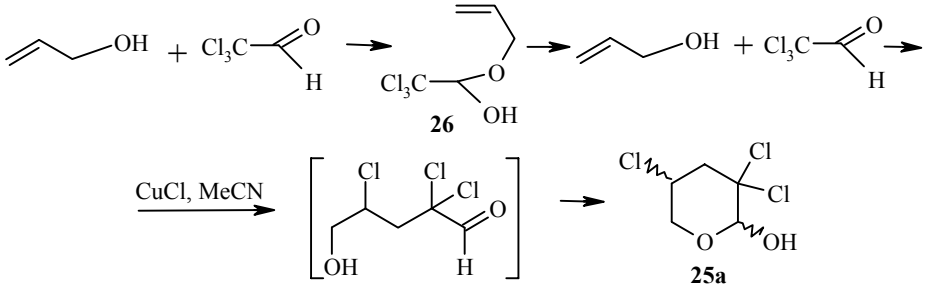
It was recently established [24, 25] that the addition of chloral to allyl alcohols containing a terminal double bond leads to the formation of polychlorinated 2-hydroxytetrahydropyrans as mixtures of diastereomers:



25a–e

25 a $R^1 = R^2 = H$; **b** $R^1 = H$, $R^2 = Me$; **c** $R^1 = R^2 = Me$;
d $R^1 = H$, $R^2 = Et$; **e** $R^1 = Cl$, $R^2 = H$

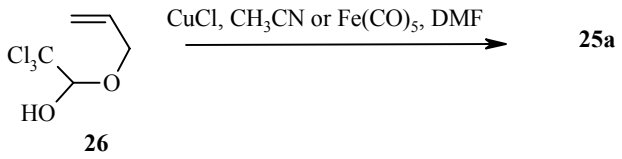
It was shown [25, 26] that the reaction of chloral with allyl alcohols leads initially to the formation of semiacetals, which decompose into the initial compounds under the reaction conditions (sealed tube, 130°C). In the presence of a copper-containing catalyst the trichloromethyl group of the chloral attacks the carbon of the carbonyl group, leading to the formation of a pyran ring:



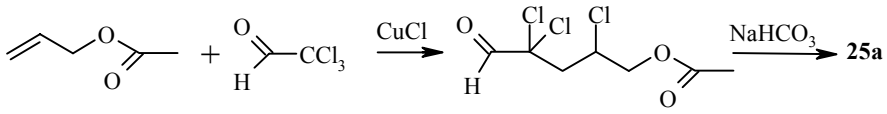
26

25a

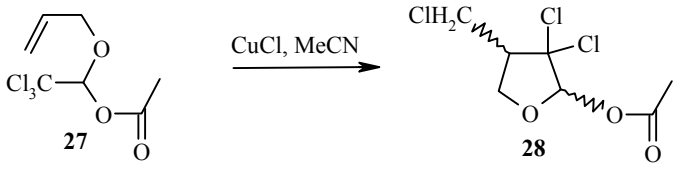
The specially synthesized semiacetal of chloral and allyl alcohol enters similarly into cyclization with the formation of tetrahydropyran. This process is catalyzed by salts of copper(I) or by iron pentacarbonyl [27]:



This compound is also formed during the hydrolysis of 5-acetoxy-2,2,4-trichloropentanal, obtained by the addition of chloral to allyl acetate:

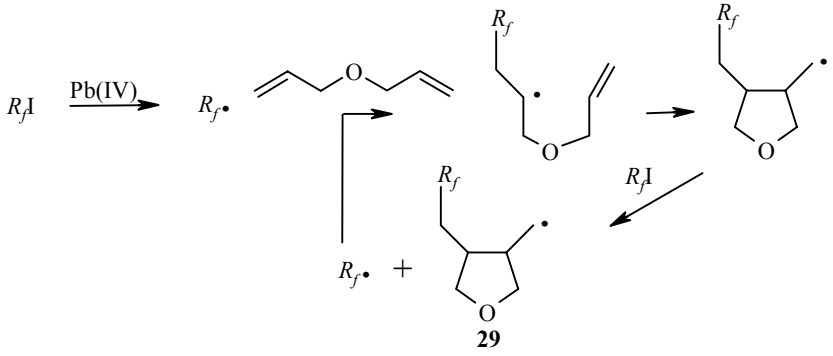


It is necessary to mention that the cyclization of specially obtained 1-allyloxy-2,2,2-trichloroethyl acetate (**27**), incapable of the dissociation that is possible in the case of the unprotected acetal, leads to the formation of 2-acetoxy-3,3-dichloro-4-chloromethyltetrahydrofuran (**28**) [26]. In our opinion this indicates a radical mechanism of addition of the chloral to the double bond of the allyl alcohol.



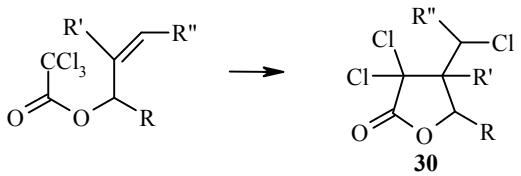
2.2. Furan-containing Compounds

Five-membered rings – tetrahydrofurans – are formed during the reaction of perfluoroalkyl iodides with diallyl ether in the presence of lead tetraacetate or dioxide [28]:



The formation of five-membered rings during the addition of polyhalides to unsaturated oxygen-containing compounds serves to confirm that the reaction takes place by a mechanism including the intermediate formation of radical particles.

An important method of forming polychlorinated tetrahydrofurans is the intramolecular addition of the trichloromethyl group to the double bond in allyl trichloroacetates [23]:

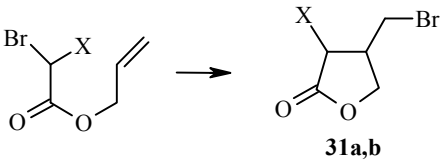


30

In this paper the effects of the catalyst, solvent, reaction time, and temperature on the yield of the product from cyclization of the allyl trichloroacetate and on the ratio of the amounts of five- and six-membered rings were investigated. The obtained data are given in Table 2.

The stereochemistry of cyclization was also investigated. It was shown that the ratio of *cis*/*trans* isomers is determined not by the stereochemistry of the alkene but by the size of the substituent at the double bond. The *trans* isomer is formed preferentially. An exception is the cyclization of 2-cyclohexenyl trichloroacetate. In this case the reaction product, formed with a yield of 38%, has *cis*-fusion of the rings.

The cyclization of allyl bromoacetate and allyl α-bromopropionate, initiated by iron pentacarbonyl, also leads to the corresponding γ-lactones [29]:



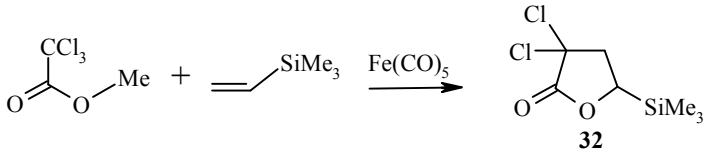
31a,b

31a X = Br, **b** X = Me

TABLE 2. The Ratio of the Amounts of Five- and Six-membered Rings Depending on the Conditions of Cyclization of Allyl Trichloroacetate [23]

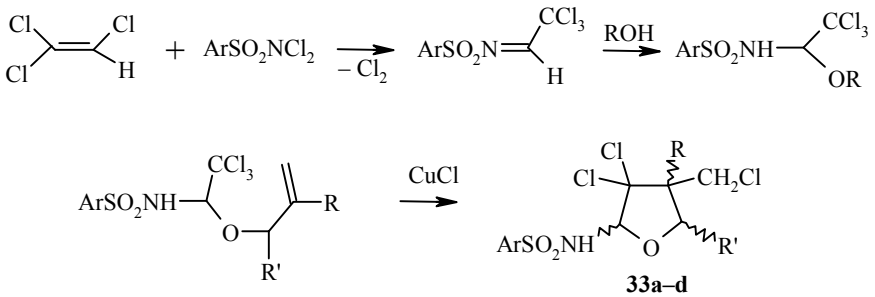
Catalyst, mole %	CH_3CN, mole/l	T, °C	Time, h	Conversion of ester	Yield, %	
					furan	pyran
$RuCl_2(Ph_3P)_3$ (2)	0.75	110	16	90	0	13
$RuCl_2(Ph_3P)_3$ (2)	0.75	110	16	92	0	24
$Cp_2Mo_2(CO)_6$ (2)	0.75	110	16	38	0	6
CuCl (2)	0.75	110	16	72	34	2
CuCl (2)	0.75	110	16	21	3	8
CuCl (2)	0.75	110	16	40	19	0
CuCl (20)	0.75	110	16	97	59	0
CuCl (30)	0.75	110	16	98	95	0
CuCl (30)	0.25	110	16	99	99	0
CuCl (30)	0.13	140	2.5	95	95	0
Cu_2O (2)	0.75	110	16	49	27	1
$Cu(NO_3)_2$ (2)	0.75	110	16	68	47	1
Cu(CCPh) (2)	0.75	110	16	78	65	0
$Fe(CO)_2$ (2)	0.75	110	16	46	16	2
$Fe_2(CO)_9$ (2)	0.75	110	16	9	3	2
$Cp_2Fe_2(CO)_4$ (2)	0.75	110	16	15	1	2

During the addition of methyl trichloroacetate to vinyltrimethylsilane, initiated by metal carbonyls in the absence of nucleophilic additions (DMF, HMPTA), 3,3-dichloro-5-trimethylsilyl-γ-butyrolactone was isolated as the main product [30]:



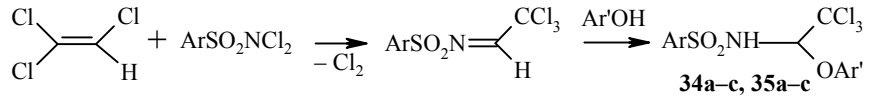
32

As already mentioned in the previous section, the cyclization of the acylated chloral allyl semiacetal in the presence of copper monochloride leads to the formation a tetrahydrofuran ring. Other derivatives of chloral containing an unsaturated fragment enter into an analogous reaction. Thus, the action of heat on chloral allylsulfamino acetals in the presence of copper monochloride makes it possible to obtain 3,3-dichloro-4-chloromethyl-2-sulfaminotetrahydrofurans (**33a-d**) [26]:



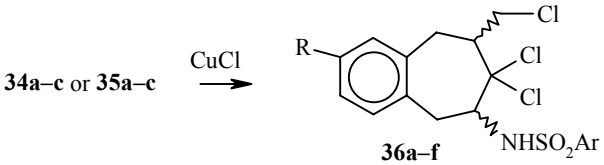
33a–d

By using chloral instead of the allyl alcohols of *ortho*-allylphenols in the reaction with sulfimines it is possible to synthesize 3,3-dichloro-4-chloromethyl-2-sulfaminobenzoxepins with satisfactory yields (20-30%) as mixtures of diastereomers:



34a–c, 35a–c

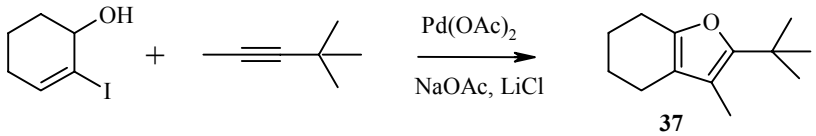
34 Ar' = 2-allylphenyl, 35 Ar = 2-allyl-4-methylphenyl



36a–f

36a R = H, Ar = Ph; **b** R = H, Ar = 4-MeC_6H_4; **c** R = H, Ar = 2-$O_2NC_6H_4$; **d** R = Me, Ar = Ph; **e** R = Me, Ar = 4-MeC_6H_4; **f** R = Me, Ar = 2-$O_2NC_6H_4$

Recently [31] it was established that vinyl halides add to acetylenes in an acetate buffer solution. Appropriately substituted alcohols were used in this reaction to synthesize furan derivatives with yields of 60-70%, for example:



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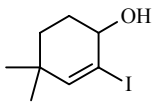
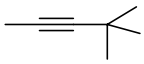
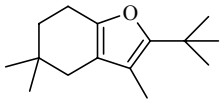
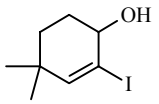
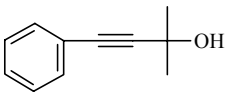
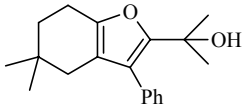
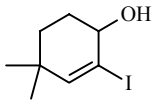
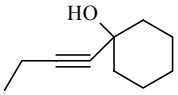
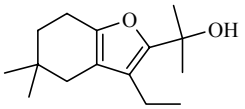
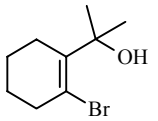
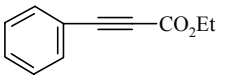
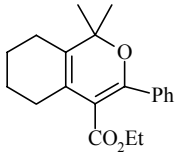
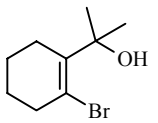
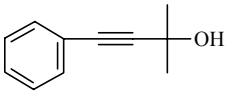
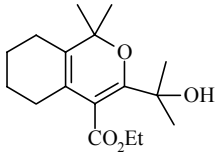
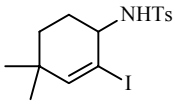
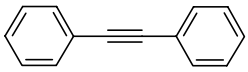
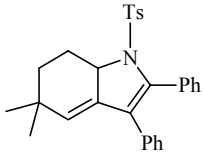
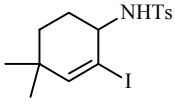
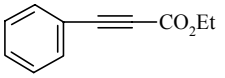
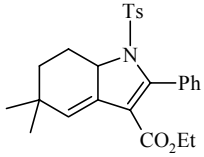
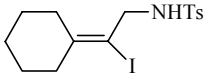
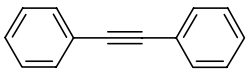
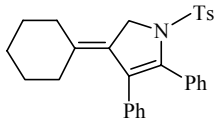
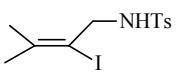
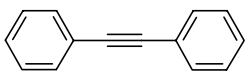
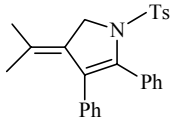
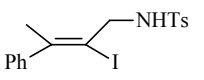
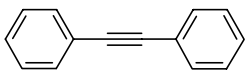
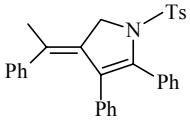
Nitrogen-containing heterocycles can also be synthesized by this method. Examples of the synthesis are given in Table 3.

The examples clearly demonstrate the significance of the investigated Kharasch reaction in the synthesis of heterocyclic compounds.

TABLE 3. Examples of the Synthesis of Five-membered Heterocyclic Compounds from Vinyl Halides and Alkynes [31]

Halide	Alkyne	Product	Yield, %
			69
			72
			51
			61
			48
			78
			64
			58
			77
			61

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