

Mini Review





Selective alkylation of organic compounds

Abstract

In this paper are presented the results on the selective alkylation of polyfunctional compounds in our research group under conditions of phase transfer catalysis as examples of regioselective alkylation of phenol, aldehyde and ketone, diketone as acetoacetic acid derivatives, malonic ether, acetylacetone (O and C alkylation), ethanolamine (O and N alkylation) and of selectivity for mono- and dialkylation alkylation of primary amid of carbonic acid as acetoamide and acrylamide. The special attention is given to alkylation of very widespread organic molecule-ethanolamine, however on alkylation reaction poorly studied. The conditions for selective and regioselective alkylation are retrieved on the basis of obtained data combination. Depending on a constitution of studied substrate alkylation reaction in basic medium is expedient for conducting or in phase transfer catalysis conditions or at the presence of dipolar solvents. In a number of cases the high selectivity of alkylation reaction is provided a thermal alkylation of organic acid with the quaternary ammonium salt, as a carrier of alkyl group. The formulated scientific conditions open new capabilities for research of alkylation reaction of organic compounds, determine conditions directional and finding of routes for selective and regioselective alkylation.

The offered methods for selective alkylation of organic molecules in comparison with the traditional methods has more advantages:high speed of process, soft condition of reaction allowing lower of a power expenses, the complete exception of application of hazardous and dangerous organic solvents, by virtue of—it is sharp reduction of air pollution, much smaller volumes of waste water. This is of all, there are devoted to technological problems of the synthesis of more important organic compounds in the aspect of environmental protection.

Keywords: selective alkylation, regioselectivity, phase transfer catalysis, dipolar solvents, thermal alkylation, quaternary ammonium salt, polyfunctional compounds, phenol, aldehyde and ketone, diketone, amid of carbonic acid, alkyl group, ethanolamine, protection of an environment.

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Introduction

The problem of an effective utilization of initial materials in chemical conversion had, has and will have a principal importance in chemistry and chemical technology. The continuously becoming complicated nature of new synthetic problems awakes the chemists to elaborate the new approaches to implementation already of known conversions and to create in essence new methods of transformation of organic molecules. Such researches set in essentially common vector of development of organic chemistry. High selectivity and speed of a chemical reaction at little energy consumptions, in devices of feasible sizes, become the basic criterion of prospects of chemical process from the practical point of view.

The problem of selectivity is relevant for organic synthesis, that it merits detail discussion as an independent problem. Any organic compound is multifunctional, that makes a problem of selectivity of reactions key for planning of organic synthesis.

In the present paper is given an attention to synthetic methods, which are provide possibility to control of selectivity of conversions on an example of alkylation reactions. We attempt to esteem unique capabilities for design of organic molecules and to tell about how to cause hidden and insensible molecules to react by the manner desirable for us.

Here are presented the examples of an alkylation of phenol, aldehyde and ketone, diketone as acetoacetic acidderivatives, malonic ethers, acetylacetone; ¹ ethanolamine and primary amid of carbonic acids with usage of possible methods for improvement of selectivity and regioselectivity. The special attention is given to alkylation of very widespread organic molecule – ethanolamine (colamine), however on alkylation reaction poorly studied.

Experimental part

Allyl phenyl ether synthesis

The synthesis of allyl phenyl ether is carried out by interaction of allyl bromide with phenol at the presence of dried powdered potassium hydroxide anhydrous KOH and TEBACh triethylbenzylammonium chloride in anhydrous toluene. The molar ratio of of phenol:allyl bromide:KOH:TEBACh =1:1:1,5:0,1.Toluene for 0,1 mol reagent is 20 ml.

The allyl bromide was brought in flask with phenol, TEBACh, KOH. The temperature of reaction medium is 60°C. The reaction product removes by diethyl-ether and was dried on MgSO₄. Reaction products were analyzed by chromatograph.

For gaze-liquid chromatography (GLCh)method here are used with the heat conductivity detector; columns from stainless steel





in the size 2m x 3mm;the additionals-7 %, silicon elastomer E-301 on chemosorbe AW-HMDS (0,26-0,36 mm),15 %Carbovax 20M on Chromatone N-AW-HMDS (0,126-0,160 mm) and 5 % E-30 on chromatone DMCS (0,400-0,630 mm);gas-carrier-helium (speed of 30-60 ml/mines) temperature of columns 40-240.

The products are identified using TLC method as well. Silufol UV-254 plates are used The eluente for TLC was $\rm C_6H_6$:EtOH (2:1 volume ratio) mixture. The spots are developed by iodine vapors.

The isolated products are identified by IRS (specord IR-75) and NMR (Varian "mercury-300" RS) methods. The chemical shifts are expressed by ppm with respect to $Si(CH_3)_4$. The solvent was $CDCl_3$.

It has been obtained the residues on traces consists by other allylation products of phenol as C-allylated products of allylphenyl ether –allylether of o-allylpheniol and p-allylphenol.²⁻⁴

N-allylethanolamine

The mixture of reactants - ethanolamine:allyl bromide 1:1 and cesium hydroxide 10% (in experience 2-with cesium hydroxide and ТБАБ-5мол of %, in experience 3.-With tetra methyl ammonium hydroxide 10мол of %) introduced to a reaction flask with biunique bulb supplied by a reflux condenser, dropping funnel, intensively hashed dropwise adding allyl bromide. During an adding of allyl bromide the temperature of reaction mixture has mounted up to 60°C. This temperature supported during 3h. Then a reaction mixture chilled till 10-15 °C and triply abstracted by a diethyl ether (or chloroform). The obtained extract is dried above MgSO₄. The yield of alkylation products is updated outgoing from the data GLCh, with the method of internal normalization, in matching with known samples. N-allylethanolamine b.p. 96-98°C/25MM, n^D₂₀ 1,4637, d_4^{20} 0,8964, IR spectrum: 980,1630, 3020 (CH=CH2),3200-3400 (OH, NH), NMR: 3,62m (2H, CH,CH,OH); 2,65T (2H, NCH,CH,); 3,18 (2H, CH,CH=CH,); 3,5c (1H, OH); 4,95-6,25m (3H, CH=CH,). The analysis - is founded %: C 59,29; H 10,75; N 13,97. C₅H₁₁NO. Is computed of %: C 59, 41; H 10, 89.N13,86.

Results and discussion

Previously was studied the regioselective alkylation of ambident phenol anion. Is has been established, that phenol alkylation by allyl bromide in PTC "liquid - liquid" system results at the formation of a number products with predominance of allylphenyl ether. The exclusive formation last almost from 90 % by the yield takes place in a system" solid phase-liquid "with usage of powdered, dehydrated potassium hydroxide.^{1,2}

It is known, that PTC alkylation of similar anions takes place in two phase medium at transition of anion from water or solid phase in organic phase. If there is a water environment, even with a powder of customary potassium hydroxide up to 10 % of moisture, the transition of the regenerated anion with a water shell with water molecule takes place. The last more overlaps oxygen, the most hydrated center of ambident anion and reaction particulate flows past on carbon, that is takes place carbon-alkylation with formation of allylphenol and its

derivative.²⁻⁴ With the waterless potassium hydroxide exclusively formed allylphenylether by 90 % yield.

Such weep of reaction is possible during an absence of hydrated shell around. The absence of water around oxygen reacting center of ambident anion does not create alkylation such obstacle in process.

The alkylation reaction results for formation amylphenyl ether an exclusively by 98 % yield during the transition from soft alkylating agent as allyl bromide to hard amyl bromide.

It's known that the value of the O/C-ratio depends on three factors: the polar effect of the alkyl substituents in the alkylating agents, the steric effect of the alkyl groups and the symbiotic effect of the leaving groups.³

OH + CH₂=CHCH₂Br OCH₂CH=CH₂ +
$$\begin{array}{c} CH_2CH=CH_2\\ + \bigcirc OCH_2CH=CH_2\\ + \bigcirc OCH_2CH=CH_2\\ + \end{array} + \begin{array}{c} CH_2CH=CH_2\\ + OCH_2CH=CH_2\\ + OCH_2CH=CH_2\\ + \end{array} + \begin{array}{c} CH_2CH=CH_2\\ + OCH_2CH=CH_2\\ + OCH_2CH=$$

The relative contribution of the first two effects depends on the leaving group nature. Here is a same leaving group as bromine anion and not the strong steric effect. In this case the important role has here alkyl group and that have fine explanation from HSAB concept.⁴

The powdered waterless potassium hydroxide is fine agent in a selective alkylation of methylcyclohexanone and 2-methylpropanal isobutyraldehyde and 2-ethylhexanal. But in this case the reaction with higher selectivity—the formation of monomethylated products of mentioned substrate - 2,2 dimethylcycloxanone (7) had a place with powdered waterless potassium hydroxide in the dimethoxyethane DME. The higher selectivity was obtained with benzyl bromide as alkylated agent (11) – the yield 70%.⁵

$$+ CH_{3}J \longrightarrow 7 + W$$

$$+ W$$

$$+$$

3

The alkylation of acetone and benzylmethylketone phenyl-2-propanone/ in the presence of powdered waterless potassium hydroxide by soft alkylating agent allylbromide secure higher selectivity for monoallylation—for acetone monoallylated (12):diallylated (13) ratio is 6:1 at 60°C with the common yield is 70%, for benzylmethylketone the same ratio is 9:1 at 25-30°C with the common yield is 70%. The reaction was passed in the DME and in argon flow for prevention oxidation of formed enolates.¹

$$CH_{3}-C-CH_{3} + BrCH_{2}CH=CH_{2} \longrightarrow$$

$$CH_{3}-C-CH_{2}CH_{2}CH=CH_{2} + CH_{3}-C-CH(CH_{2}CH=CH_{2})_{2}$$

$$12$$

$$C_{6}H_{5}CH_{2}-C-CH_{3} + BrCH_{2}CH=CH_{2} \longrightarrow$$

$$C_{6}H_{5} - CH_{2}CH=CH_{3}$$

$$H = O$$

$$C_{6}C-CH_{3}$$

$$H = O$$

$$14$$

The alkylation of 1,3-diketones as derivatives of acetoacetic acid—diethylacetoacetic acid, N,N-dialkylamid of acetoacetic acid, ethers and amid of malonic acid, cyanacetic acid, acetylacetone was studied.^{1,2,7} The value of the O(15)C(16)-ratio depends also on three factors as in the case phenol: the polar effect of the alkyl substituent in the alkylating agents, the steric effect of the alkyl groups and the symbiotic effect of the leaving groups. Besides that, we find also that the selectivity of alkylation depends from the type of PTC system condition. The transfer from "liquid-liquid" to "solid-liquid" increased the quantity of C-alkylated products (25).

In the case of malonic acid derivatives (ethyl ether or amid) the selectivity characterizes as mono-C (17) and dialkylated products (18).

$$\begin{array}{c} O \\ C-Y \\ CH_2 \\ C-Y \\ O \end{array} + \begin{array}{c} BrCH_2CH=CH_2 \\ C-Y \\ C-Y \\ 0 \end{array} + \begin{array}{c} CH-CH_2CH=CH_2 \\ C-Y \\ 0 \end{array} + \begin{array}{c} CH-CH_2CH=CH_2 \\ C-Y \\ 0 \end{array} + \begin{array}{c} C-Y \\ C-Y \\ C-Y \\ C-Y \\ C-Y \end{array}$$

It has been studied an alkylation of primary amides of carboxylic acids acetamide and acrylamide more prone to an alkaline hydrolysis in water-basic condition.^{6–8} The purpose of the data of activities was finding of a selective route for nitrogen-alkylation of primary amides for synthesis of the relevant industrial intermediates, syntones, for example N-allylacrylamide.⁸ It is necessary to note, that before these activities were synthesized and are inserted in industry obtaining of amides of carboxylic acids from secondary by the yield 92%. Alongside with a product amide alkylation take a place the symmetrical ether formation from hydrolysis and them further alkylation by same alkylhalogenide.

It is necessary to note, that acetamide in a two phasic catalytic system" solid=liquid "underwent to di-nitrogen alkylation almost from 35 % more by the yield, while the product mono-alkylkated (19a) will be obtained 20 %. However, with benzyl chloride the product of mono-benzylation from by 26 % yield receives only.⁷ The same product (19a) with high yield receives in super-basic system (KOH in DMSO), and also at the presence of potassium fluoride.⁶

Acrylamide alkylated selectively by allyl bromide with formation—N-allylacrylamide (19b) with an yield 11,5- 34.6 % in a two phase catalytic system "solid-liquid". In such system 18-crown-6 ethere was more effectively to quaternary ammonium salt / TEBACh/. It is necessary to note, that in a system "liquid - liquid" efficiency the quaternary ammonium salt is higher than crown - about the yield of a main product — N-allylacrilamide 47,0 %, while with 18-crown-6 only 24,0 %. However, in the last system the reaction is not selective, as the parallel formation of the corresponding ether acrylic acid, the product of hydrolysis and farther allylation of acrylic acid takes place. The exclusive formation of N-allylacrylamide takes place also in the presence of potassium fluoride with the same catalysts. ⁸

O
$$\parallel$$
RC - NH₃ + BrCH₂CH=CH₂ \longrightarrow

O \parallel
R - C - N \parallel
CH₂CH=CH₂

19

O CH₂CH=CH₂
CH₂CH=CH₂
20

 $R=-CH_3$, $-CH_2CH=CH_2$, $-C_6H_5$

We regard necessary to remind about aged method as thermal alkylation of organic acids by quarternary ammonium salts as carriers of alkyl groups. Acetamide heats at 150°C with lejkotrop- dimethyl phenyl benzyl ammonium chloride or chloride of tetra (3-chlor-2-butene)ammonium will derivate extremely products mono-nitrogenalkylation of amide 21-22 up to 60 % yield. 1,6

The selectivity of mono-nitrogen alkylation of ethanolamine depends both on a stoichiometry of reactants, and from a type used alkyl halide [9]. The exclusive formation of a product N-allylethanolamine-66 % is reached in PTC "liquid - liquid" system (catalyst tetrabutyl ammonium bromide – TBAB) at a ratio of reactants: ethanolamin:allyl bromide-5:1 at 60°C for 3 hours. The exclusive formation of mono-allylated products takes place at a ratio of reactants 1:1 in presence TBAB at 85-90°C for 3 hours with an output about 70 %-with alkyl halides as amyl bromide, nonyl bromide, decyl bromide.

On our view the interplay cationof cesium with a nitrogen part of aminoethanol with formation of the conforming complex takes place. Further, in the derivate complex cesium the cation interchanges with quaternary ammonium cation that promotes further formation of nitrogen anion, which is interact with allyl bromide with formation of N-allyl ethanolamine. It is necessary to explain absence of a dialkylated product by steric hindrances at complex – formation N-allylethanolamine with cesium or tetrabutyl ammonium cation.

It was studied the alkylation of monoethanolamine with allylbromide in PTC as catalyst used tetramethyl ammonium hydroxide. It was obtained exclusively N-monoalkylated product (23).

The high yield of O- alkylation product-alkyl ether of ethanolamine,²⁴ receives in PTC "solid liquid " system with beforehand obtained of alcoholate of ethanolamine the yield of amyl ether of mono-ethanolamine 56 %, alongside with an amyl ether of N-amyl ethanolamine.

$$H_2NCH_2CH_2OK + RCI \longrightarrow H_2NCH_2CH_2OR + RHNCH_2CH_2OR + 24$$
 25
+ $R_2NCH_2CH_2OR$
 $R = -C_5H_{11}$, $-CH_2CH_2CH_2$, $-CH_2C_6H_5$

It is necessary to note, that with allyl bromide and benzyl chloride alongside with a product of O-alkylation the products of O,N and O,N,N- alkylation receive. Relevant the fact of initial formation O-alkylated product is in this case, that is quite true connected with high nucleophilty of oxygen anion, are characterized by density of population of anion and atoms by electrons in the derivated beforehand anion of colamine (0.8407) that as contrasted by nitrogen (0,4562) and oxygen.(0,1409) in free ethanolamine.

Conclusion

According the researches on regioselective alkylation of organic acids is established:

- i. Selectivity O-alkylation of phenol to produce exclusively alkyl phenyl ether findsan explanation from HSAB concept.
- ii. The powdered waterless (anhydrous) potassium hydroxide is fine alkaline for selective alkylation of organic acids as aldehides&ketones in DME and other dipolar solvents, also in PTC system "solid-liquid".
- iii. The regioselective N-mono alkylation of ethanolamine takes place in conditions of phase transfer catalysis that depends on a stoichiometry of reagents and from a type electrophile.
- iv. High regioselectivity of mono-nitrogen alkylation is provided at the presence of cesium hydroxide in conditions of phase transfer catalysis.
- v. The O-alkylation on ethanolamine promotes in PTC condition and amino-ether takes place in the system "solid-liquid" with earlier generated alcoholate with higher yield.

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Conflicts of interest

The authors declare that there is no conflict of interest.

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