Synthesis and Some Chemical Properties 2-Substituted-3 Propargilxinazolones-4

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Annotation

An accessible procedure for the preparation of 2-substituted 3-(propyl-2-yl) xinazolones-4 and their derivatives has been developed. Substitution and addition reactions have been studied.

Key words: Quinazolon-4, propargylbromide, propargyl derivatives of 2-substituted quinazolones-4.

Quinazoline derivatives, as well as compounds containing propargyl groups, are known to have herbicidal, fungicidal, pharmacological, and other actions. The introduction of substituents in positions 2 and 3 of the quinazoline ring enhances their biological activity. One of the intensively developing areas of organic chemistry is the chemistry of nitrogen-containing heterocyclic compounds, among which quinazoline derivatives occupy a priority place. Due to the presence of several reaction centers, as well as a wide spectrum of biological activity, quinozaline derivatives are increasingly attracting attention both in chemical terms and in applied terms.

Quinazolone-4 and 2-substituted quinazolones-4 as initial reagents were synthesized according to the known method [1] from anthranilic acid with an excess of formamide.

Many literature sources indicate that sodium and potassium salts of quinazolone-4, when interacting with methyl iodide [2], bromoketones [3], dialkylaminopolymethylene chlorides [4], β-chloroacrylic acid [5], form exclusively only 3-alkylquinazolone- 4.

Thus, this brief literature review shows that, despite the fact that there are methods in the literature for the preparation of various 3-substituted and 2, 3-disubstituted derivatives of quinazolones-4 with various substituents, interest in the synthesis of their new compounds does not decrease.

Propargyl-substituted quinazolones-4 were synthesized by the interaction of 2-R-quinazolones-4 with propargyl chloride or bromide according to the scheme:

where Hal = CI, Br I=III
R = H(1); CH_3(II); Ph(III)

Despite the fact that this reaction is widely used to introduce a propargyl group into the molecule, in order to find optimal conditions, we studied the effect of the nature of the solvent and halogen in the propargyl fragment on the yield of the final product, since the initial derivatives of quinazolone-4 are used in these reactions for the first time. The course of the reaction was monitored by thin layer chromatography (TLC) on a loose layer of aluminum oxide in the chloroform-benzene 4:1 system.

For the synthesis of compound 1 under the same conditions (temperature, reaction time), hexane, ether, benzene, ethanol, and acetone were used as solvents.

It turned out that the yield of the product is 42, 48, 52, 56, 84, respectively. These data show that with an increase in the polarity of the solvent, an increase in the yield of the reaction product occurs.

Our studies have shown that propargyl bromide is more reactive than propargyl chloride. This is explained by the fact that bromine has a greater mobility than chlorine, i.e., in the case of propargyl bromide, the ability to replace is much higher than that of propargyl chloride. The yield of propargyl derivatives of quinazolone-4 is also affected by the nature of the substituents in position 2 of the quinazolone ring, namely, the yield is in the series quinazolone-4 > 2-methylquinazolone-4 > 2-phenylquinazolone-4 (see Table 1.). Apparently, a slight decrease in the yield in this series can be explained by the spatial effect of the substituent in position 2.

In our case, i.e. alkylation of quinazolone-4, 2-methyl-2, 2-phenylquinazolones-4 with propargyl bromide results in the formation of only 3-propargylquinazolones-4. [6]. This behavior of these compounds can be explained by the fact that the reaction proceeds under the experimental conditions most likely via the SN2 mechanism. This is confirmed by an increase in the yield of the reaction product when using bipolar opratic solvents according to Kormblum's rule in reactions SN2-involvement occurs at the atom with a lower electron density but higher polarizability. In the quinazolone ring, this is the nitrogen atom in position 3.

Thus, for the synthesis of propargyl derivatives of quinazolones-4 in high yield, it is necessary to carry out the reaction in anhydrous acetone and use propargyl bromide rather than propargyl chloride.

The structure of the synthesized 3-propargyl-substituted quinazolones-4 was established by IR, NMR spectroscopy and mass spectrometry.

Table No. 1
Some physicochemical and spectral characteristics
2-substituted 3-(propyn-2-yl) quinazolones-4

№ connections	R	Output, %	Rf	T pl.^{0}C	ИК-спектры, υ, см$^{-1}$				
					≡C-H	C≡C	C=O	C=N	Aromatic ring of quinazolones-4
I	H	84	0,58	105-106	3220	2125	1670	1610	1600, 1560, 1475 1450, 770, 740
II	CH_3	76	0,48	74-75	3200	2130	1650	1602	1590,1565, 1480 1420, 765, 733
III	Ph	72	0,36	148-149	3240	2120	1685	1600	1590,1565,1485, 1370, 770,700

Comparative interpretation of the IR spectra of the original quinazolones-4 with 2-R-3-(propyn-2-yl)-quinazolones-4 shows that the main absorption bands characterizing the quinazolone ring remain almost unchanged. With the introduction of a propargyl group at the position of 3-quinazolone, the absorption band of the C = O group shifts to the low-frequency region by 25–45 cm–1. However, new absorption bands appear that characterize C ≡ C and ≡ C – H bonds in the regions of 2120-2130 cm-1 and 3200-3240 cm-1, respectively, which indicates the presence of a terminal acetylenic bond, which are absent in the IR spectrum of the original quinazolone-4 .

Analysis of the PMR spectrum of 2H-3-(propyn-2-yl)-quinazolone-4 shows that the equivalent protons of the aromatic ring give signals of a multiplet nature in the range of 7.10-8.62 ppm. The singlet signal according to the intensity corresponding to one proton at 8.50 ppm characterizes the proton located between two nitrogen atoms. Signals in the form of a doublet and a triplet in the region of 4.92-4.95 and 3.15-3.24 ppm. – CH2-, ≡ CH, respectively. The characteristic value of the spin-spin interaction constant is 2–3 Hz.

In the mass spectrum of compound 1, the decomposition of the molecular ion proceeds with the elimination of CO and HCN groups, which is typical for quinazolone-4 derivatives. The resulting N-propargylaniline ion is cyclized to quinoline. Further, the decay proceeds with the loss of HCN and C2H2. (see diagram).

Scheme of mass spectrometric decomposition of 3-(propyn-2-yl)
quinazolone-4

Obtaining acetylenides

The hydrogen atom at the triple bond is very mobile and is easily replaced by a metal forming acetylenides. This reaction is widely used as a qualitative reaction to identify the terminal proton.

It is known in the literature [7–8] that acetylides are intermediates for the purposeful synthesis of substances by biological activity. In this regard, we obtained acetylides of 2-substituted-3-(propyne-1)-quinazolones-4 according to the procedure [9-10] (Table 2).

The reaction proceeds at room temperature. To do this, an aqueous ammonia solution of copper chloride or an alcoholic solution of silver nitrate is added to an alcohol or alcohol-acetone solution of 3-propargyl derivatives of quinazolones-4 with vigorous stirring. The yield of acetylides was quantitative. Copper acetylenides are yellow powdery substances, and silver acetylenides are white. They do not dissolve in water, which is explained by the low polarity of the covalent bond between C-Me. In addition, there is a strong intermolecular donor-acceptor interaction in acetylides.

The structure of the acetylenides was proved by elemental analysis data, the structure by IR spectroscopy.

The results of the analysis for the content of C, H and metal are consistent with the calculated values.

The IR spectra of acetylenides differ sharply from the IR spectra of the starting propargyl derivatives of quinazolones-4.

The disappearance of the absorption band in the region of 3250 cm-1 indicates the absence of a terminal proton. With the formation of ≡ C-Cu bonds, other characteristic absorption bands, for example, C=O bonds, are slightly shifted to the high-frequency region, but their intensity does not weaken.

Thus, the new propargyl derivatives of quinazolones -4 at room temperature easily undergo the reaction of triple bond hydrogen substitution for metal, forming acetylenides in quantitative yields.

Table 2

Physicochemical constants of acetylenides of 2-substituted-3-(propin-2-il) quinazolones-4

№ connections	R	Me	T.pl.0C	Acetylene color	Found %, Me	Gross formula	Calculated %, Me
IV	H	Cu	168-169	yellow	25,60	$C_{11}H_7N_2OCu$	25,75
V	CH_3	Cu	178-179	yellow	24,10	$C_{12}H_9N_2OCu$	24,39
VI	Ph	Cu	191-192	yellow	19,46	$C_{17}H_{11}N_2OCu$	19,68
VII	H	Ag	176-177	White	36,85	$C_{11}H_7N_2OAg$	37,04
VIII	CH_3	Ag	182-183	White	35,24	$C_{12}H_9N_2OAg$	35,37
IX	Ph	Ag	197-198	White	29,24	$C_{17}H_{11}N_2OAg$	29,38

Halogenation

It is known that many compounds having the functional group -C ≡ C - Hal have herbicidal and fungicidal properties.

Therefore, the synthesis of new gel-substituted 3-propargyl derivatives of quinazolones-4 is topical.

To obtain haloacetylenes, the hypohaloid method [19] of substitution of acetylenic hydrogen is used. We have obtained new 2-substituted (H, CH3, C6H5)-3-(3-halopropin-2-yl) quinazolones-4 by this method.

Where, HaI = Br or J

R = H, CH_3, Ph

The composition of halogenated propargyl derivatives of quinazollones-4 was determined by elemental analysis, and their structure was confirmed by IR spectroscopy. An analysis of the IR spectra shows that the presence of absorption bands in the regions of 2150, 1680, 700-500 cm-1 characterizes the functional groups C ≡ C, C = O, C-Hal, respectively. In addition, the disappearance of the absorption band of the stretching vibration ≡ CH bond at 3250 cm-1 indicates the expected structures of the compounds.

Thus, the method for the synthesis of 2H-, 2-methyl-2-phenyl-3-(3-halopropyn-2-yl)quinazolones-4 by the hypohalide method has a number of advantages over other methods.

Присоединение галогенов

Despite the large amount of literature data on the addition of a halogen to a triple bond, these reactions have their own characteristics in each individual case. This is related to the degree of polarization of the triple bond.

It is known that the addition of bromine to alkynes often proceeds at room temperature with the formation of tetrabromo derivatives at the ratio of reagents bromine:quinazolone-4-2:1. Therefore, we studied the addition of bromine to propargyl derivatives of quinazolone-4 in acetic acid at room temperature according to the scheme.

Where R = H, CH_3, Ph

The obtained 2H, 2-methyl-, 2-phenyll-3 (2,2,3,3-tetrabromo) propylquinazolones are white powdery substances, poorly soluble in organic solvents.

In the IR spectrum of the compound 2H-3(2,2,3,3-tetrabromopropylquinazolones, there are no absorption bands at 3220, 2125 cm-1 characteristic of the stretching vibrations ≡ C – H and C ≡ C bonds, respectively.

The absorption bands of the amide carbonyl and N = C bonds of the quinazolone ring ($_{\nu}$C = O, $^{\gamma}$N = C) are shifted by 50 cm-1 to the high-frequency region compared to the initial 3-propargyl derivative of quinazolones-4. In the IR spectrum, new absorption bands appear at 550 cm-1, indicating the formation of a C-Br bond.

Thus, propargyl derivatives of quinazolones-4 easily add two molecules of bromine and form tetrabromo derivatives of quinazolones-4.

Hydration reaction

It has been established that the addition of water to alkynes in an acidic medium in the presence of catalysts (salts of copper (1) or mercury (II) leads to the formation of snols, which, due to instability, quickly isomerize into ketones. Similarly, we studied the hydration of 2H, 2-methyl- , 2-phenyl-3-propargylquinazolone-4. The isolated substances are white crystals, readily soluble in acetone, dioxane, DMF, DMSO, but insoluble in water and ether. The solubility of the resulting ketones decreases in the series: H, CH3, Ph.

To confirm the structure of the obtained ketones, their IR spectra were taken. A comparative analysis of the IR spectra of the starting and final compounds shows that the disappearance of the absorption bands at 3220 cm-1 and 2125 cm-1 characterizing the stretching vibrations ≡ CH and C ≡ C bonds, respectively, indicates the hydration of the acetylene bond. The presence of an absorption band of medium and strong intensities at 1720 cm-1 and 11672 cm-1 indicates the presence of two carbonyl (C = O) groups in the molecule. The absorption band of medium intensity at 1720 cm-1 corresponds to the stretching vibrations of the carbonyl group of acyclic ketones. At the same time, the absorption band of the quinazolone carbonyl group of strong intensity at 1679 cm-1, as well as other absorption bands characterizing the quinazolone cycle, remain almost unchanged.

Thus, 3-propargyl-2H, 2-methyl-2-phenyl quinazolones-4 readily react with hydration and form ketones with quinazolone substituents. The resulting 2H, 2-methyl-, 2-phenyl-3-acetonyl (or propane-2-OH)-quinazolones-4 are not described in the literature.

Thus, a systematic study was carried out on synthesis and chemical transformations (replacement of the hydrogen of the acetylene residue in position 1, etc.). 2-substituted-3-propargylquinazolones-4 and simple convenient methods have been developed for the preparation of 2-substituted 3-(propyn-2-yl)-quinazolones-4, 3-tetrabromopropyl-, acetonitrile -.

It has been shown that alkylation of 2-H,2-methyl-,2-phenylquinazolones-4 with propargyl bromide proceeds selectively with the nitrogen atom in position 3 affected.

The addition reactions of bromine and water at the triple bond of 2-H, 2-methyl-, 2-phenyl-3-(propyn-2-yl)-quinazolones-4 have been studied. It was revealed that their bromination is accompanied by the formation of exclusively tetrabromo-substituted ones. As a result of hydration, quinazolone-4 keto derivatives were synthesized for the first time.

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