

REACTION OF 2-HETARYL-2-(TETRAHYDRO-2-FURANYLIDENE)ACETONITRILES WITH ALDEHYDES

O. V. Khilya^{1*}, Ya. V. Baglay¹, and Yu. M. Volovenko¹

The reaction of 2-hetaryl-2-(tetrahydro-2-furanylidene)acetonitriles with a electrophilic reagent (anisaldehyde) was studied. It was shown that condensation of the latter with 2-(4-oxo-3,4-dihydro-2-quinazolyl)- and 2-(1H-benzo[d]imidazol-2-yl)-2-(tetrahydro-2-furanylidene)acetonitriles in the presence of secondary amines or acids takes place with elimination of the furan fragment and the formation of 3-aryl-2-(4-oxo-3,4-dihydro-2-quinazolyl)- and 2-(1H-benzo[d]imidazol-2-yl)acrylonitriles.

Keywords: 2-(1H-benzo[d]imidazol-2-yl)acetonitrile, 2-(1H-benzo[d]imidazol-2-yl)-2-(tetrahydro-2-furanylidene)acetonitriles, 2-(4-oxo-3,4-dihydro-2-quinazolyl)acetonitrile, 2-(4-oxo-3,4-dihydro-2-quinazolyl)-2-(tetrahydro-2-furanylidene)acetonitriles.

Earlier we described the synthesis of 2-hetaryl-2-(tetrahydro-2-furanylidene)acetonitriles **1a** [1-4] and **1b** [2-4] starting from the corresponding 6-chloro-2-(hetarylidene)-3-oxohexanenitriles. It is known that the reaction of (2Z)-(dihydro-2(3H)-furanylidene)acetonitriles with electrophilic reagents and with DMF dimethyl acetal in particular takes place at position 3 of the furan system with the formation of 2-{3-[(E)-1-dimethylaminomethylene]tetrahydro-2-furanylidene}acetonitrile [5, 6].

While continuing research into the reactions of furanylideneacetonitriles with electrophiles we studied the reaction of 2-hetaryl-2-(tetrahydro-2-furanylidene)acetonitriles **1a,b** with anisaldehyde (**2**).

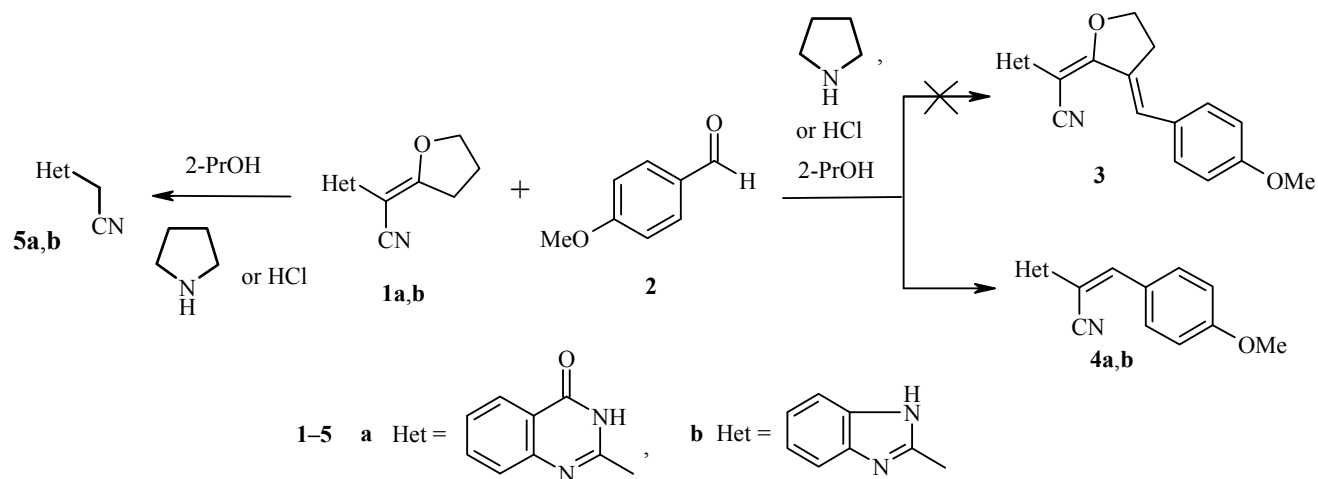
The reaction of compounds **1a,b** with the aldehyde **2** was conducted by heating in 2-propanol in the presence of pyrrolidine. However, the expected condensation products **3a,b** were not detected in the reaction products. The structure of styrenes **4a,b** was assigned to the products on the basis of data from elemental analysis and ¹H NMR, IR, and mass spectra. Further evidence for such a structure is the absence of a melting point depression in a mixed melting test with a sample of compound **4a** and the styrene obtained by the previously described method [7].

Compounds **4a,b** were obtained with yields of 78 and 84% respectively. In the ¹H NMR spectra of the styrenes **4a,b** the signals of the aromatic protons are observed in the region of 7.1-8.2 ppm, and those of the methine protons at 8.3-8.4 ppm.

* To whom correspondence should be addressed, e-mail: olgakh@univ.kiev.ua.

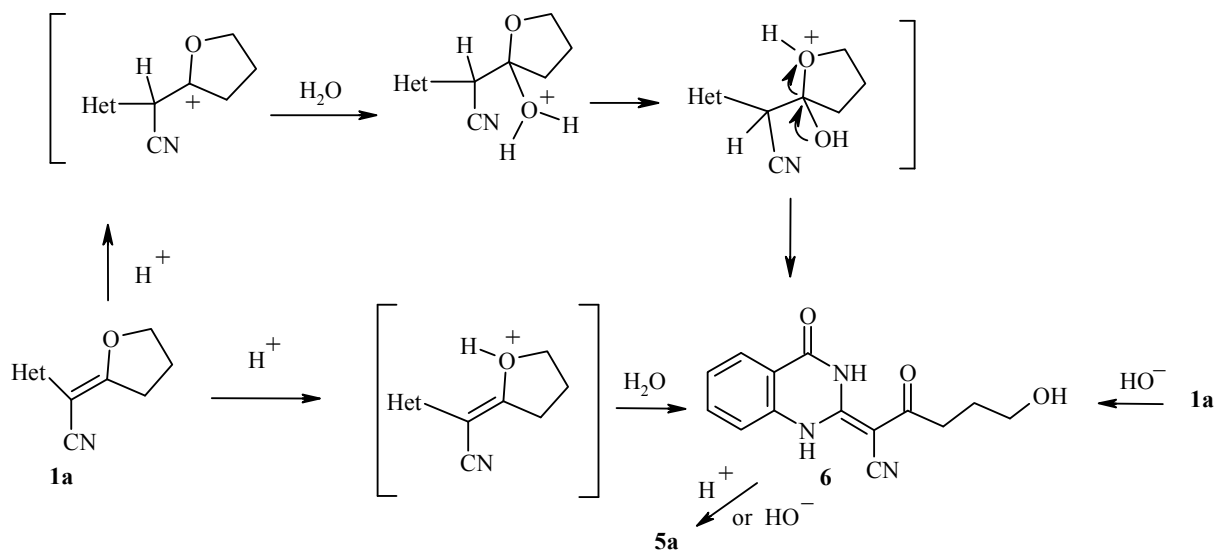
¹Taras Shevchenko Kiev National University, Kiev 01601, Ukraine.

By realizing the reaction in the presence of various catalysts it was possible to establish that the formation of compounds **4a,b** can be catalyzed by both acids and bases. It was shown that the products **4a,b** are formed both in the presence of pyrrolidine and in the presence of hydrochloric acid. When *p*-toluenesulfonic acid or triethylamine were used as catalysts the initial compounds **1a,b** were isolated unchanged.



A similar transformation of 2-cyano-3-methylcrotonic ester in reaction with benzaldehyde in the presence of piperidine, which catalyzes cleavage of the C=C bond of the crotonic fragment, was described in [8]. The obtained methyl cyanoacetate then condenses with the aldehyde. From the examined mechanism it follows that the corresponding hetarylacetonitrile **5a,b** must be formed in the reaction of compounds **1a,b** with the aldehyde **2** in the presence of pyrrolidine or HCl; by condensing with the anisaldehyde this will give the styrene **4a,b**. When the reactions were carried out without the aldehyde the hetarylacetonitriles **5a,b** were formed [9, 10].

The obtained facts make it possible to suppose that the last transformation may correspond to the following scheme of transformations:



On the basis of the transformations of 2-(4-oxo-3,4-dihydro-3-quinazoliny)-2-(tetrahydro-2-furanylidene)acetonitrile **1a** it can be assumed that the intermediate product in this chain is the product **6** (produced by the action of the alkalis on the derivative **1a**), which can then split with the formation of the acetonitrile **5a**. The last transformation can be realized by heating an alcohol solution of compound **6** in the presence of an acid or a base.

The structure of the product **6** was confirmed by data from the ^1H NMR and IR spectra. In the ^1H NMR spectra in the region of 7.4-8.0 ppm there are signals for the protons of the quinazoline ring. In the downfield region there are broad signals for two protons exchanging with the D_2O : at 12 ppm for the 1-NH proton and at 14 ppm for the 3-NH proton (forming an intramolecular hydrogen bond with the C=O group of the acyl residue). The signals for the protons of the methylene groups of the acyl fragment appear in the region of 1.7-3.5 ppm. The H-8 proton of the quinazoline undergoes a paramagnetic shift (compared with the value of the latter for compound **1a**) and is observed in the form of a significantly broadened signal, possibly indicating the presence of exchange interaction with the 1-NH proton, the signal of which is broader than the signal of the 3-NH proton.

In the IR spectra there is an absorption band for the C=O group of the quinazoline ring at 1690 cm^{-1} and at 1645 cm^{-1} there is a band for the conjugated C=O group of the acyl fragment of the molecule taking part in the formation of a hydrogen bond. The stretching vibrations of the conjugated C \equiv N group are observed at 2210 cm^{-1} . Absorption in the region of $3400\text{-}2900\text{ cm}^{-1}$ is due to the NH bonds of the quinazolinone ring and the OH group.

The structure of compounds **5a,b** was confirmed by data from the ^1H NMR spectra, IR spectra, and elemental analysis, which fully agree with data for the previously obtained compounds [9, 10]. There was no melting point depression in a mixed melting test with compounds **5a,b** and the previously obtained compounds [9, 10].

Thus, it was established as a result of the investigations that when alcohol solutions of 2-hetaryl-2-(tetrahydro-2-furanylidene)acetonitriles are heated in the presence of secondary amines or acids the furan fragment is split and subsequently eliminated, leading to the formation of the respective 2-hetarylacetonitriles.

EXPERIMENTAL

The IR spectra were recorded on a Perkin-Elmer Spectrum BX instrument (for compound **5a** on a Unicam SP 3-300 Pye instrument) in DMSO-d_6 with TMS as internal standard. The reactions and the purity of the products were monitored by TLC on Silufol UV-254 plates in the 9:1 chloroform-methanol system. The melting points were measured on small-scale heater bench of the Boetius type with the VEB Analytik PHMK observation device.

3-(4-Methoxy)-2-(4-oxo-3,4-dihydro-2-quinazoliny)- and 2-(1H-Benzo[d]imidazol-2-yl)-3-(4-methoxy)- acrylonitriles **4a and **4b**.** To a mixture of the compound **1a,b** (1.2 mmol) and aldehyde **2** (0.18 g, 1.3 mmol) in 2-propanol (10 ml) we added 3-4 drops of pyrrolidine (or 2-3 drops of hydrochloric acid). The mixture was heated for 1-2 h until the initial compound **1** had disappeared (according to TLC). The pH of the reaction mixture was then brought to 7. The precipitate was filtered off, washed with water and with alcohol, and dried. A small quantity of the product **4a,b** can be isolated from the mother liquor by adding 5-10 ml of water.

Compound 4a. The yield 78%; mp $293\text{-}295^\circ\text{C}$ (mp $293\text{-}295^\circ\text{C}$ [7]). IR spectrum, ν , cm^{-1} : 3440 (NH), 2224 (C \equiv N), 1675 (C=O). ^1H NMR spectrum, δ , ppm (J , Hz): 3.88 (3H, s, 4- CH_3O); 7.19 (2H, d, $^3J = 8.5$, H-3,5 Ar); 7.56 (1H, t, $^3J = 8.0$, H-6); 7.72 (1H, d, $^3J = 8.0$, H-8); 7.86 (1H, t, $^3J = 8.0$, H-7); 8.02 (2H, d, $^3J = 8.5$, H-2,6 Ar); 8.15 (1H, d, $^3J = 8.0$, H-5); 8.43 (1H, s, =CH-Ph); 12.55 (1H, br. s, NH). Found, %: N 13.71. $\text{C}_{18}\text{H}_{13}\text{N}_3\text{O}_2$. Calculated, %: N 13.85.

Compound 4b. The yield 84%; mp 223-225°C. IR spectrum, ν , cm^{-1} : 3434 (NH), 2224 ($\text{C}\equiv\text{N}$). ^1H NMR spectrum, δ , ppm (J , Hz): 3.88 (3H, s, 4- CH_3O); 7.17 (2H, d, $^3J = 8.5$, H-3,5 Ar); 7.25 (2H, m, H-5,6); 7.61 (2H, m, H-4,7); 8.01 (2H, d, $^3J = 8.5$, H-2,6 Ar); 8.28 (1H, s, $=\text{CH}-\text{Ph}$); 13.00 (1H, br. s, NH). Found, %: N 15.30. $\text{C}_{17}\text{H}_{13}\text{N}_3\text{O}$. Calculated, %: N 15.26.

2-(4-Oxo-3,4-dihydro-2-quinazolinyl)- and 2-(1H-Benzo[d]imidazol-2-yl)acetonitriles 5a and 5b. To compound **1a,b** (1.2 mmol) in 2-propanol (10 ml) we added 3-4 drops of pyrrolidine (or 2-3 drops of hydrochloric acid). The mixture was heated for 1-2 h until the initial compound **1** had disappeared according to TLC. The pH of the reaction mixture was then brought to 7. The precipitate was filtered off, washed with water, and dried. A small quantity of the product **5a,b** can be isolated from the mother solution by adding 5-10 ml of water. The yield of compound **5a** was 92%, and the yield of compound **5b** was 87%.

(2E)-6-Hydroxy-2-(4-methylene-3,4-dihydro-2(1H)-quinazolidene)-3-oxohexanenitrile (6). To a suspension of compound **1a** (0.51 g, 2 mmol) in ethanol (or 2-propanol) (20 ml) we added 1.04 ml of a 10% aqueous solution of NaOH. The mixture was boiled for 2-3 h while the end of the reaction was monitored by chromatography. The reaction mixture was cooled, and the pH of the mixture was brought to 7. The precipitate was filtered off, washed with water and with alcohol, and dried. A small quantity of the product **6** can be isolated from the mother solution by adding 10 ml of water. The yield 88%; mp 221°C. IR spectrum, ν , cm^{-1} : 2900-3400 (NH, OH), 2210 ($\text{C}\equiv\text{N}$), 1690 ($\text{NHC}=\text{O}$), 1645 ($\text{C}=\text{O}$), 1600 ($\text{C}=\text{CCN}$). ^1H NMR spectrum, δ , ppm (J , Hz): 1.75 (2H, m, $\text{CH}_2\text{CH}_2\text{CH}_2$); 2.68 (2H, t, $^3J = 7.6$, COCH_2); 3.44 (2H, t, $^3J = 6.3$, CH_2OH); 4.31 (1H, br. s, OH); 7.38 (1H, t, $^3J = 7.8$, H-6); 7.74 (1H, t, $^3J = 7.8$, H-7); 7.8 (1H, br. s, H-8); 8.0 (1H, d, $^3J = 7.8$, H-5); 11.56 (1H, br. s, 1-NH); 13.97 (1H, br. s, 3-NH). Found, %: N 15.35. $\text{C}_{14}\text{H}_{13}\text{N}_3\text{O}_3$. Calculated, %: N 15.49.

2-(4-Oxo-3,4-dihydro-2-quinazolinyl)acetonitrile (5a). To compound **6** (0.43 g, 1.6 mmol) in 2-propanol (15 ml) we added 30% aqueous solution of NaOH (0.2 ml) (or 2-3 drops of hydrochloric acid). The mixture was heated for 1-2 h until the initial compound **6** had disappeared according to TLC. The pH of the reaction mixture was then brought to 7. The precipitate was filtered off, washed with water and with alcohol, and dried. A small quantity of the product **6** can be isolated from the mother solution by adding 10 ml of water. The yield was 83%.

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