Chimica Techno Acta
published by Ural Federal University
eISSN 2411-1414; chimicatechnoacta.ru

LETTER
2022, vol. 9(1), No. 20229103
DOI: 10.15826/chimtech.2022.9.1.03

Features of –C–C– coupling of quinoxaline-2-one with ethyl acetoacetate under acid catalysis

Yu.A. Azev *, O.S. Koptyaeva, A.A. Mkrtchyan, T.A. Pospelova

Ural Federal University, 620002 Mira st., 19, Ekaterinburg, Russia
* Corresponding author: azural@yandex.ru

This short communication (letter) belongs to the Regular Issue.

Abstract

Quinoxalin-2-one (1) reacts with ethyl acetoacetate in trifluoroacetic acid (TFA) to form 3-(2-oxopropylideno)-3,4-dihydroquinoxaline-2-one (2) and 3-(3-oxo-3,4- dihydroquinoxaline-2-(1H)-ylidene)methylquinoxaline-2-(1H)-one (3). The reaction product 3 was also obtained by heating the compound 1 with acetone in the presence of TFA.

Keywords

quinoxaline-2-one
ethyl acetoacetate
nucleophilic substitution of hydrogen
vicarious substitution
acid catalysis

Received: 16.11.2021
Revised: 11.01.2022
Accepted: 11.01.2022
Available online: 14.01.2022

Key findings

- The replacement of hydrogen led to the formation of water, which activated the process of cleavage of the dicarbonyl group of 3-(2-oxopropylideno)-3,4-dihydroquinoxaline-2-one. The acyl group of com pound 3-(2-oxopropylideno)-3,4-dihydroquinoxaline-2-one was "vicarious" in this reaction.
- The formation of 3-(3-oxo-3,4-dihydroquinoxaline-2-(1H)-ylidene) methylquinoxaline-2-(1H)-one was the result of C,C-coupling of compounds quinoxaline-2-one and 3-(2-oxopropylideno)-3,4-dihydroquinoxaline-2-one, similarly to the reaction of quinoxaline-2-one 1 with acetone.

1. Introduction

Compounds with various types of biological activity were found among quinoxaline derivatives. [1, 2] Quinoxidine and Dioxidine were used as antimicrobial agents [3].

The features of the synthesis and biological activity of quinoxaline derivatives are described in the review [4]. It was previously reported that quinoxaline salts interact with acetylacetone or ethyl acetoacetate in the presence of base catalysis (diethyl and triethylamines) to form 3a,4,9,9a-tetrahydro-*endo*-furo[2,3-b]quinoxalines [5].

The authors of the article [6] described the cyclization of 1,3-bis(silyl-enol-ethers) and quinoxaline with the formation of 6-alkylidene-2,3-benzo-1,4-diaza-7-oxobicyclo[4,3,0]non-2-yenes. There were known examples of hydrogen substitution in the heterocyclic nucleus of quinoxaline when the reactions with various C-nucleophiles were carried out in the presence of acid. As a result, –C–C-coupling products were obtained [7].

Recently [8] it was found that quinoxaline-2-one reacted with acetylacetone, benzylacetone, and heptane-3,5-dione when heated in TFA to form derivatives 6a,7-dihydropyrido[1,2-a]quinoxaline-6,8-dione.

Examples of reactions of aliphatic aldehydes with quinoxalin-2-one in the presence of acid with the formation of 6-oxidopyrido[1,2-*a*]quinoxalinium zwitter ions were published [9].

It was also previously found that when quinoxalin-2-one and phenylhydrazine hydrazones are heated in butanol in the presence of TFA, hydrogen substitution products are formed [10].

It should be noted that there have been no data on –C–C– coupling of quinoxaline-2-one with esters of β-dicarbonyl acids in the literature.

2. Experimental

Unless otherwise indicated, all common reagents and solvents were used from commercial suppliers without further purification.

The reaction progress and purity of the obtained compounds were controlled by thin layer chromatography

(TLC) method on Sorbfil UV-254 plates, using visualization under UV light. Melting points were determined on a Stuart SMP10 melting point apparatus.

^{1}H, ^{13}C and ^{19}F NMR spectra were acquired on Bruker Avance-400 and Bruker Avance NEO–600 spectrometers in DMSO-d_6 solutions, using TMS as internal reference for ^{1}H and ^{13}C NMR or $CFCl_3$ for ^{19}F NMR. Mass-spectra (EI, 70 eV) were recorded on MicrOTOF-Q instrument (Bruker Daltonics) at 250 °C.

Elemental analysis was performed using a Perkin-Elmer 2400 Series II CHNS/O analyzer.

2.1. Reaction of quinoxaline-2-one 1 with ethyl acetoacetate

A mixture of quinoxaline-2-one (**1**) (0.2 mmol) and ethyl acetoacetate (0.6 mmol) was refluxed in 2.0 ml of TFA at 110 °C in a sealed vessel for 50 hours. The solvent was removed *in vacuo*. The precipitate was dissolved in ethanol (3.0 ml). The alcoholic solution was treated with water (2.0 ml) followed by treatment with 15% NH_4OH solution to pH 7–8 with the formation of a precipitate. The precipitate of the mixture of reaction products was filtered off.

3-(2-Oxopropylidene)-3,4-dihydroquinoxaline-2-one (2) was isolated using preparative chromatography (R_f = 0.156, Silica gel Kiselgel 60 PF 254, chloroform).

Yield 35%, m.p. 267–268 °C ([11] 267 °C). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.19 (*s*, 3H), 6.06 (*s*, 1H), 7.08–7.13 (*m*, 3H), 7.37–7.40 (*m*, 1H), 11.86 (*s*, 1H), 12.96 (*s*, 1H). MS (IR, 70 эВ), *m/z* ($I_{отн}$, %): 202 (M^+, 100), 187 (M-15, 98), 159 (M-43, 60). Found, %: C 65.28; H 4.99; N 13.88. $C_{11}H_{10}N_2O_2$. Calculated, %: C 65.34; H 4.98; N 13.85.

3-(3-oxo-3,4-dihydroquinoxaline-2-(1*H*)-ylidene)methylquinoxaline-2-(1*H*)-one (3) was isolated by preparative chromatography (R_f = 0).

Yield 5%, m.p. >300 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.87 (*s*, 1H), 7.16–7.21 (*m*, 6H), 7.71–7.73 (*m*, 2H), 11.93 (*s*, 2H), 13.62 (*s*, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 88.91, 99.49, 115.16, 121.09, 123.29, 125.18, 128.28, 128.54, 147.03, 155.71. MS (EI, 70 eV), *m/z* ($I_{отн}$, %): 304 (M^+, 100), 276 (18), 248 (27). Found, %: C 67.13; H 3.99; N 18.38. $C_{17}H_{12}N_4O_2$. Calculated, %: C 67.10; H 3.97; N 18.41.

2.2. Reaction of quinoxaline-2-one 1 with acetone

0.5 mmol of quinoxaline-2-one (**1**) was heated with 0.6 mmol of acetone in a mixture of butanol (2 ml) and TFA (0.5 ml) at 110 °C in a sealed vessel for 25 hours. The solvent was removed *in vacuo*. The precipitate was suspended in ethanol (3 ml) and filtered off. The resulting precipitate of 3-(3-oxo-3,4-dihydroquinoxaline-2(1*H*)-ylidene) methylquinoxaline-2-(1*H*)-one (**3**) was recrystallized from DMSO and dried.

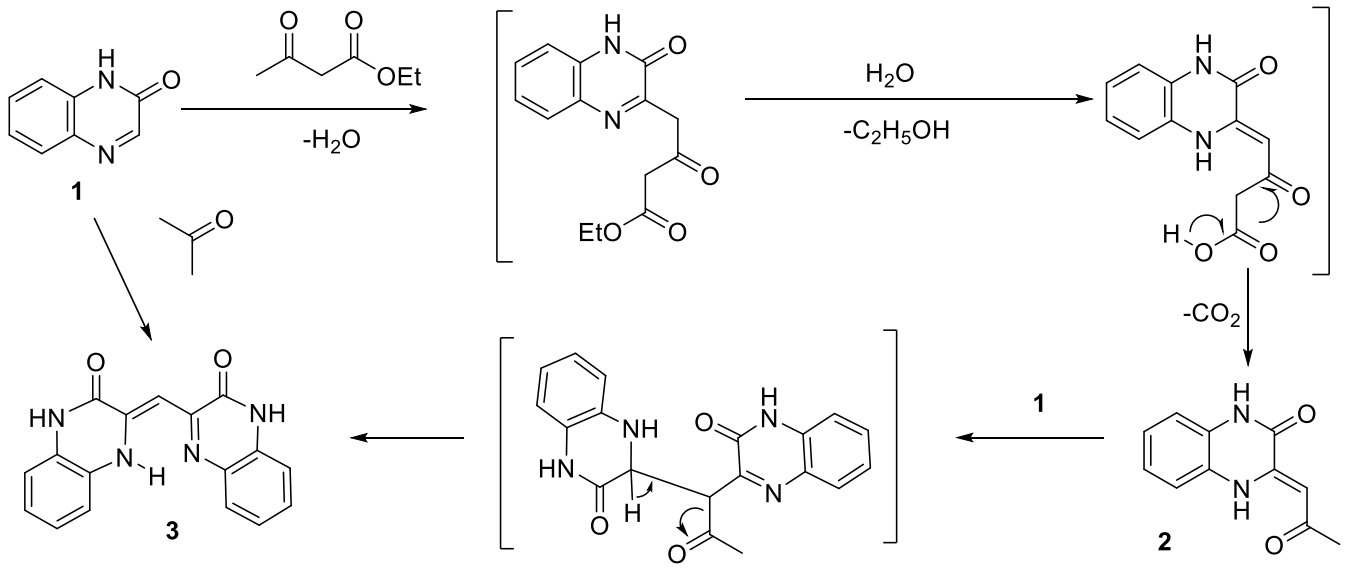
Yield 30%. The melting point and spectral characteristics of the reaction product were similar to those obtained in the product of the interaction of quinoxaline-2-one (**1**) with ethyl acetoacetate.

3. Results and discussion

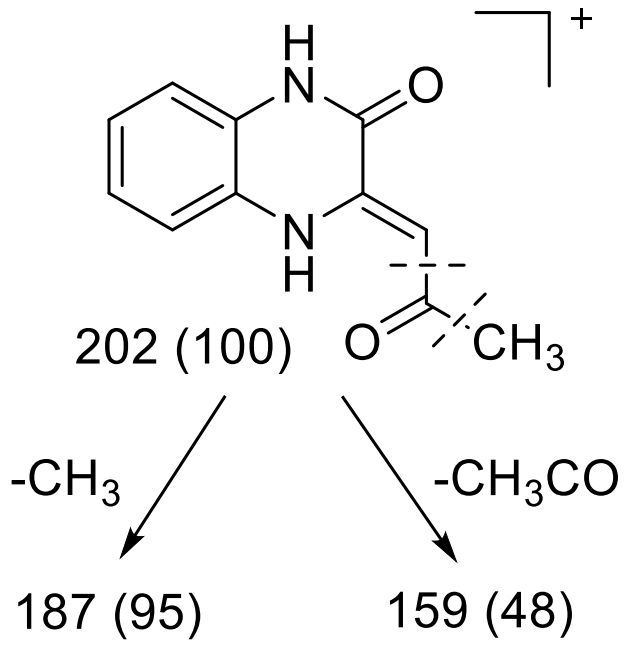
While developing effective methods for the functionalization of quinoxaline-2-one, we investigated the interactions of quinoxaline-2-one with ethyl acetoacetate under acid catalysis. We found that heating the reagents in TFA resulted in the formation of 3-(2-oxopropylideno)-3,4-dihydroquinoxaline-2-one **2** (Scheme 1).

The mass spectrum of compound **2**, in addition to the molecular ion peak, contained intense peaks of ions with molecular weights of 187 (M–CH_3) and 159 (M–$COCH_3$). These peaks were formed during the decomposition of ketones, which were characteristic of these compounds in common (Scheme 2).

The singlet of the protons of the methyl group in the NMR spectrum of compound **2** in DMSO-d_6 was observed at 2.3 ppm. The signal of the proton of the methine group of the enamine fragment was observed at 6.2 ppm.



Scheme 1 The formation of 3-(2-oxopropylideno)-3,4-dihydroquinoxaline-2-one 2



Scheme 2 The decomposition of ketones to form molecular ions

It could be assumed that the formation of the reaction product **2** proceeded through a number of stages: nucleophilic substitution of hydrogen, hydrolysis of the ester group, and decarboxylation with the formation of the final product.

Obviously, the replacement of hydrogen led to the formation of water, which activated the process of cleavage of the dicarbonyl group of compound **2**.

In addition to the compound **2**, 3-(3-oxo-3,4-dihydroquinoxaline-2-(1*H*)-ylidene) methylquinoxaline-2-(1*H*)-one **3** was found in the reaction products.

In the mass spectrum of compound **3**, an intense peak with *m*/*z* 304 was observed. It corresponded to the proposed structure.

The ^{1}H NMR spectrum of compound **3** contained the characteristic signal of the proton of the enamine fragment at 6.9 ppm. A two-proton singlet of two amide NH-groups was observed at 11.9 ppm. The singlet of the NH group of the quinazoline nucleus appeared in a weak field at 13.7 ppm. The shift of this signal was apparently due to the presence of a hydrogen bond between the NH group of quinazoline and the N-atom of another quinoxaline nucleus.

The formation of compound **3** was the result of –C–C– coupling of quinoxaline-2-one **1** with a new C-nucleophilic agent, which was formed during the reaction, compound **2**. Apparently, the acyl group of compound **2** was "vicarious" in this process.

The ompound **3** was also obtained by heating the compound **1** in acetone in the presence of TFA.

Obviously, the formation of **3** was the result of C,C-coupling of the compounds **1** and **2**, similarly to the reaction of quinoxaline-2-one **1** with acetone.

4. Conclusions

In conclusion, it should be noted that the synthesis of alkylated derivatives of quinoxaline-2-one was carried out earlier [11] by the interaction of 1,2-dihydroquinoxaline 4-oxide with active methylene compounds in the presence of piperidine. Nevertheless, direct alkylation of quinoxaline-2-one with ethyl acetoacetate under conditions of acid catalysis was described by us for the first time.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

1. Barlin GB. The Chemistry of Heterocyclic Compounds: The Pyrazines. New York: Wiley-VCH; 1982. 687 p. doi:10.1002/9780470187173
2. Cheeseman GWN, Cookson RF. The Chemistry of Heterocyclic Compounds: The Condensed Pyrazines. New York: Wiley-VCH; 1979. 843 p.
3. Mashkovsky MD. Lekarstvennyye sredstva [Medicines]. Moscow: Nauka; 1993. 347 p. Russian.
4. Sakato G, Makino K, Kurasawa Y. Recent progress in the quinoxaline chemistry. Synthesis and biological activity. Heterocycles. 1988;27(10):2481–515. doi:10.3987/REV-88-397
5. Chupakhin ON, Charushin VN, Klyuev NA, Rezvukhin AI, Semion VA. Cyclization of N-alkylazinium cations with bisnucleophiles. 3.endo adducts in the reaction of quinoxalium salts with β-diketones and their x-ray diffraction analysis. Chem Het Comp. 1981;17:1046–52. doi:10.1007/BF00503539
6. Schmidt A, Guetlein J-P, Langer P. Synthesis of 6-alkylidene-2,3-benzo-1,4-diaza-7-oxabicyclo[4.3.0]non-2-enes by cyclization of 1,3-bis(silyl enol ethers) with quinoxalines. Tetr Let. 2007;48:2067–2069. doi:10.1016/j.tetlet.2007.01.147
7. Azev YuA, Kodess MI, Ezhikova MA, Gibor AM, Baranov VI, Ermakova OS, Bakulev VA. New opportunities for the synthesis of quinoxaline-substituted heterocyclic and aryl moieties. Pharm Chem J. 2013;9:498–502. doi:10.1007/s11094-013-0989-z
8. Azev YuA, Kodess MI, Ezhikova MA, Ermakova OS, Berseneva VS, Bakulev VA. Reactions of quinoxaline-2-one with β-diketones: a new approach to 6a,7-dihydro-5H-pyrido[1,2-a]quinoxaline-6,8-diones. Mend Comm. 2017;1:97–98. doi:10.1016/j.mencom.2017.01.032
9. Azev YuA, Ermakova OS, Berseneva VS, Kodess MI, Ezhikova MA, Ganebnykh IN. Synthesis of the 6-oxidopyrido[1,2-a]quinoxalinium derivatives from quinoxaline-2-one and aldehydes – new examples of domino reactions. Mend Comm. 2017;27:637–639. doi:10.1016/j.mencom.2017.11.034
10. Azev YuA, Koptyaeva OS, Tsmokalyuk AN, Pospelova TA, Bakulev VA. Benzaldehyde phenylhydrazones as C-nucleophiles for functionalization of quinoxaline-2-one. Unusual transformations of indole-3-carbaldehyde phenylhydrazones. AIP Conf Proc. 2020;2280:0018799. doi:10.1063/5.0018799
11. Tennant G. Heterocyclic N-oxides. Part II. Nucleophilic reactions of 1,2-Dihydro-2-oxoquinoxaline 4-oxide. J Chem Soc. 1964;1982–1986.