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KABACHNIK-FIELDS REACTIONS WITH 2,3-TRIMETHYLENE-1,2,3,4- TETRAHYDROHINAZOLON-4

Annotation

In the article synthesized 2,3-trimethylene-3,4-dihydrohinazolon from anthranilic acid and pyrrolidone-2 in the presence different agents, such as PCl_5 , $POCl_3$. Its reduction reaction with $NaBH_4$ carrying out. Obtained 2,3-trimethylene-1,2,3,4-tetrahydrohinazolon this three-component coupling of a carbonyl, an amine and a hydrophosphoryl compoud leads to α-aminophosphonates, phosphorous acid-formaldehyde; aldehydes in three component system; aminomethylphosphonic acid synthesis based on kabachnik-filds reaction. 2,3- trimethylene-3,4-dihydrohinazalon 55% da product obtained. The reason of low reaction yield was studied. Structures were confirmed using IR and ^1H NMR spectroscopies. Obtained product reduced using $NaBH_4$ and 2,3-trimethylene-1,2,3,4-tetrahydrohinazolon synthesis was carried out with high yield. 2,3- trimethylene-1,2,3,4-tetrahydrohinazolon and respective aminophosphonic acids were synthesized in three component system with high yield.

Keywords: 2,3-trimethylene-3,4-dihydrohinazolon, 2,3-trimethylene-1,2,3,4-tetrahydrohinazolon, anthranilic acid, pyrrolidone-2, Kabachnik–Filds reactions & IR spectra

2,3-TRIMETILEN-1,2,3,4- TETRAGIDROXINAZOLON-4 BILAN FOSFIT KISLOTANING KABACHNIK-FILDS REAKSIYALARI

Annotatsiya

Maqolada 2-aminobenzoy kislotasi va pirrolidon-2 dan turli xil moddalar, masalan, PCl_5, $POCl_3$ ishtirokida 2,3-trimetilen-3,4-digidrobenzo[2,3-d]pirimidin-4-on sintez qilingan. Uning $NaBH_4$ bilan qaytarilish reaksiyasi amalga oshirilgan. Olingan 2,3-trimetilen-1,2,3,4-tetragidrobenzo [2,3-d]pirimidin-4-on - karbonil, amin va gidrofosforil birikmasining uch komponentli birikmasi a-aminofosfonatlarga olib keladi, fosfat kislotasi-formaldegid; uch komponentli sistemadagi aldegidlar; aminometilfosfon kislota sintezi kondensatsiya reaksiyasiga asoslangan. 2,3- trimetilen-3,4-digidrobenzo[2,3-d]pirimidin-4-on 74% da mahsulot olindi. Reaksiya maxsulotining unumi qayta sintezlarda oshirildi. Tuzilmalar IR va 1H NMR spektroskopiyalari yordamida tasdiqlangan. $NaBH_4$ yordamida qaytarilgan va 2,3-trimetilen-1,2,3,4-tetragidrobenzo[2,3d]pirimidin-4-on sintezidan olingan mahsulot yuqori unum bilan amalga oshirildi. 2,3-trimetilen-1,2,3,4-tetragidrobenzo[2,3-d]pirimidin-4-on va tegishli aminofosfon kislotalar uch halqali molekula yuqori unum bilan sintez qilindi.

Kalit so‘zlar: 2,3-trimetilen-3,4-digidrobenzo[2,3-d]pirimidin-4-on, 2,3-trimetilen-1,2,3,4-tetragidrobenzo[2,3d]pirimidin- 4-on, 2-Aminobenzoy kislotasi, pirolidon-2, Sintez reaktsiyalari va IQ spektrlari.

РЕАКЦИИ КАБАЧНИК-ПОЛЕЙ С 2,3-ТРИМЕТИЛЕН-1,2,3,4-ТЕТРАГИДРОХИНАЗОЛОН-4

Аннотация

В статье синтезирован 2,3-триметилен-3,4-дигидрохиназолон из антраниловой кислоты и пирролидона-2 в присутствии различных агентов, таких как PCl5, POCl3. Проведение реакции его восстановления с использованием $NaBH_4$. Получен 2,3-триметилен-1,2,3,4-тетрагидрохиназолон. Трехкомпонентное соединение карбонила, амина и гидрофосфорильного соединения приводит к α-аминофосфонатам фосфористой кислоты-формальдегида; альдегиды в трехкомпонентной системе; Синтез аминометилфосфоновой кислоты на основе реакции Кабачника-Филдса. Получен 2,3-триметилен-3,4-дигидрохиназалон 55% да продукта. Изучена причина низкого выхода реакции. Структуры подтверждены методами ИК- и ЯМР 1Н-спектроскопии. Полученный продукт восстановлен с помощью NaBH4 и синтез 2,3-триметилен-1,2,3,4-тетрагидрохиназолона проведен с высоким выходом. 2,3-триметилен-1,2,3,4-тетрагидрохиназолон и соответствующие аминофосфоновые кислоты синтезированы в трехкомпонентной системе с высоким выходом.

Ключевые слова: 2,3-триметилен-3,4-дигидрохиназолон, 2,3-триметилен-1,2,3,4-тетрагидрохиназолон, антраниловая кислота, пирролидон-2, реакции Кабачника–Филдса и ИК-спектры.

Introduction. In the world synthesis of new physiologically active derivatives of hinazolon and creation on their basis of modern medicinal facilities come with the use of high-tech. It is known that the anti-cancer drugs applied to date, destroying malignant cancer cells, simultaneously damage healthy cells.

Representatives of hinazolons is preferentially operating anti-cancer drugs of palbocyclik, preparations of antibacterial action of pipemidic and piromid acids are worked out by the world scientists. These medical facilities promote practical interest in derivatives.

Organophosphous compounds are ubiquitous in nature and find applications in the fields of agriculture, medicine, and industry [1-3]. Some organophosphorus compounds are important pesticides [4], bactericides [5-7], and antibiotics [5]. Phosphorus analogues of α-pyrones act as HIV protease inhibitors [8]. α-aminophosphonic acids constitute important motifs

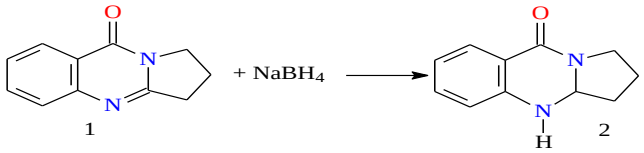
among the organophosphorus compounds in medicinal chemistry due to their obvious structural similarities to α-amino acids [9,10]. Many natural and synthetic aminophosphonic acids and their ester and peptide derivatives display a wide range of biological activities [11,12], act as herbicides [13], enzyme inhibitors [14], and antibacterial [15,16] antiviral [10], and antitumor [17] agents, and may even be peptide mimics [18]

The most common synthetic route to α-aminophosphonic acids is via chemical manipulation of the corresponding α-aminophosphonates [19-21]. The hydrophosphonylation of imines is a widely used method for the synthesis of α-aminophosphonates [19-27]. This is achieved by one of two pathways: (I) in a two-component fashion known as the Pudovik reaction [28,29] or (II) by the Kabachnik-Filds reaction [22, 23, 30, 31] which combines in situ formation of imine by condensation of amines with an aldehyde or ketone and an hydrophosphonylation step [32]. One-pot Kabachnik-Filds reaction can be promoted by acidic or basic catalysts, microwave irradiation, or by heating [33]. Due to the above–mentioned factors, in this paper we reported the synthesis of αaminophosphonates with high yield using a recyclable catalyst for applications in medicine and industry.

Materials and methods. Threecyclic 2,3-thremetilen-3,4-dihydrohinazalon(1) was synthesized coming from anthranilic acid that was exposed to condensation with pyrrolidone-2 in the presence of $POCl_3$.

Scheme 1: Synthesis of 2,3-trimethylene-3,4-dihydrohinazalon-4

Yield of products of condensation with lactam row 2-aminotiophen-3-carboxylic, 2- aminobenzoyic (antranilic) and 2-aminopyridin-3-carboxylic acids go down. So, if 2,3-threemetylentieno[2,3-d]- pyridin-4-one is got with 81% yield, and 2,3-polymetylen-3,4-dihydrohinazalon - with 56-70% yield, in the cases of 2,3- thremetylenhinazalon (1) he made a 35%. This fact explained by that π-electron a surplus tiophenic ring facilitates, and π-deficit bhynzol ring hampers flowing of this condensation. In infrared spectrum 1 there are absorptions bands characteristic for amido carbonyl groups (N-C=O) in area of 1683 cm^{-1}, and absorption bands of C_2=N_1 double bond show up in area of 1625 cm^{-1}. In 1H NMR spectrum 1 ($CDCl_3$) aromatic protons are observed in the weak fields at 7.31-7.34 ppm in a kind duplicate of duplicates (^{1}H, dd, J=4.6, 7.9, H-6), 8.48-8.53 (^{1}H, ppm J=2.0, 7.9, H-5) and 8.86-8.89 (^{1}H, ppm, J=2.0, 4.6, H-7). Selective reduction of N_1=C_2 bonds. Reduction of 2,3-thremetyleno-3,4-dihydro by the hinazalon-4 (1) borhydrid of natrium in a spirit solution at boiling results in formation of 2,3-thremytilen-1,2,3,4- tetrahydrohinazalon-4 (2). In this case, selective reduction goes N_1=C_2 to double bonds of anthranilic ring, and carbonyl group C=O in position 4 remains.



Scheme 2. Reactions of 1 with NaBH4

ESI-MS the spectrum of product of reaction gives a strong band of molecular [M+H] ion at m/z 190, that specifies on molecular mass of this fragment 189, and along with ^{1}H NMR results spectral data leads to the molecular formula of $C_{10}H_{11}N_3O$.

After reduction a 1 absorption band at 1625 cm^{-1} (C=N) disappears in IR spectrum (2). The absorption band of carbonyl group at C_4, that reveals at 1718 cm^{-1} (CO) in initial connection, is displaced toward lowfrequency areas (1654 cm^{-1}). Saturated N_1 appears as a result of selective restoration-C_2 bond (product of reduction 2).

In ^{1}H NMR spectrum 2 signals of protons α- and β- CH_2 of groups appear in area of 1.85-2.40 (4H) as multiplet, unlike initial bonds [3.20 (2H, trip, J=7.9, α- CH_2), 2.26 (2H, quar., β-CH_2).

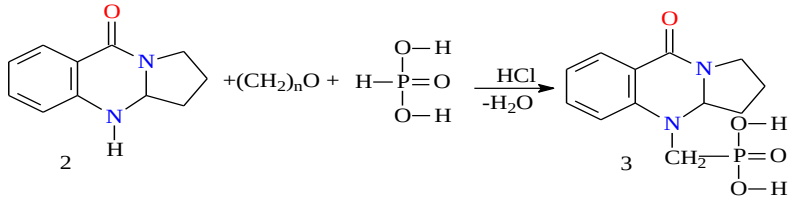
Signals of protons-CH_2 groups showing up in areas 3.59 (^{1}H, td, J=8.6; 2.9, γ a-CH_2) and 3.70 (^{1}H, m, γ e-CH_2) also differ from the signals of analogical protons in initial connection [4.16 (2H, t, J=7.3, γ- CH_2)].

Here becomes obvious circumstance that recovery of N1=C2 is connections to HN-CH results in noticeable displacement of chemical changes of protons of methylene groups toward the strong fields. Found out also substantial displacement of signals of protons of pyridinic ring after reduction. So, in initial step they appear at ppm: 7.34 (^{1}H, dd, J=4.6, 7.9, C6-H), 8.53 (^{1}H, dd, J=2.0, 7.9, C5-H), 8.89 (^{1}H, dd, J=2.0, 4.6, C7-H), accordingly; and in the product of renewal the same protons are observed in areas: 6.74 (^{1}H, dd, J = 5.0; 7.6, C6- H), 8.06 (^{1}H, dd, J=1.8; 7.4, C5 - H) and 8.10 (^{1}H, dd, J=1.8; 5.0, C7-H), accordingly; i.e. and here is displacement of chemical changes of protons toward the strong fields. Proton of asymmetric carbon of C2-H found out at 5.10.

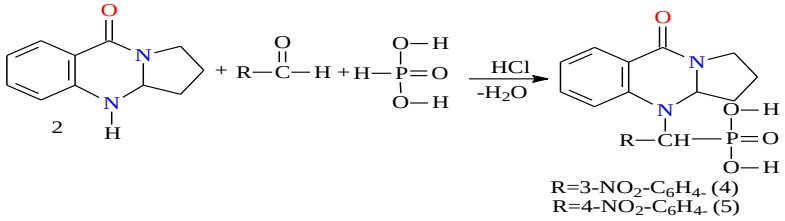
In the initial experiments, the one-pot, three-component reaction of 2,3-trimethylene-1,2,3,4- dihydrohinazolon-4, p and m-nitro-benzaldehyde, and phosphorous acid was chosen as the model reaction to optimize the reaction conditions. In the present work, the procedures followed for the synthesis of α-aminophosphonates are conventional shown in Table-1, entries 3-5. The products α-aminophosphonates were obtained by solvent-free microwave irradiation of aldehyde, amine, and phosphorous acid for 1 min. In toluene, without any catalyst, the product formed was in a good yield.

Thin layer chromatography (TLC) was employed to monitor reaction progress and to determine the purity of the products. The reaction was carried out using catalytic amount of HCl, in toluene for 30 min. All the title compounds are readily soluble in polar organic solvents.

The IR spectra of compounds (3-5) showed the N-CH_2 band in the range of 1550 cm^{-1}. The sharp band observed in the range 1240–1291 cm^{-1} is due to the νP=O, and a band for P–C stretching occurred in the range 740– 770 cm^{-1}. All the stretching frequencies are compiled in Table 2. ^{1}H NMR spectra of the compounds (3-5) were recorded in the DMSO-d6 solvent. The aromatic protons of α-aminophosphonic acids appeared as a multiplet in the region δ 6.15–8.69. The P–C–H group proton resonated as a multiplet in the range δ 3.77–4.86.



Scheme 3. Reaction with Paraforum



Scheme 4. Reaction with Aromatic Aldehyde

Table 1: Reaction time and percentage yield of 2 in Different Reaction Condition

Entry	Catalyst used	Reaction condition	Reaction time	yield
3	HCl	Toluene/reflux	3	83
4	HCl	Toluene/reflux	3	86
5	HCl	Toluene/reflux	3	89

In toluene, without any catalyst, the product formed was in a good yield, but the time taken was 4 to 5 h, which is considerably longer.

Table 2: Elemental Analysis and IR data of Compounds (1-5)

№	Mol. formula	Elemental analysis found (Calc)			IR spectral data in cm^{-1}			
		C	H	N	C=O	P=O	P-O	P-C
1	**$C_{10}H_9N_2O$**	68,46	4,96	24,55	1718			
2	**$C_{10}H_{11}N_2O$**	66,28	5,81	22,56	1760			
3	**$C_{11}H_{14}N_2O_4P$**	54,65	4,92	16,74	1695	1210	1040	751
4	**$C_{18}H_{20}N_3O_6P$**	50,16	4,61	14,46	1670	1268	1070	745
5	**$C_{18}H_{20}N_3O_6P$**	50,16	4,61	14,46	1685	1263	1030	763

EXPERIMENTAL DETAILS.

Synthesis of hydrochloride of 2,3-trimethylene-3,4-dihydrohinazalon-4 (1).

$POCl_3$ (90 ml) was dropped to mixture of anthranilic acid (65.3 g, 0.47 mol) and pyrrolidone-2 (47.94 g, 0.564 mol) by stirring at room temperature. Reaction mixture heated at 80-90ºC for 4 hours, cooled to room temperature and added 100 ml water. Aqueous solution worked up by 5% NaOH solution to pH 7.5-8. Extracted by chloroform (3x100 ml) and organic phase dried with Na_2SO_4, filtrated and evaporated solvent. Yield of compound 1 is 30.76 g (35%), m.p. 139-140ºC. R_f 0.48 (10:1 chloroform-methanol).

To solution of a 28,05 g (0,15 mol) 2,3 - trimethylene - 3,4 - dihydrohinazalon- 4 (1) in 350 mls of alcohol added a 30 g (0,78 mot) of sodium borohydride. Reaction mixture was boiled on water bath during 3H and left on a 1 twenty-four hours. A solvent was driven away, remaining product was dissolved in water and left for 1 hour. Falling out sediment was filtered washed 3 times water, dried and recrystallized from a hexane. Yield of compound 2 is 28.35 g (91%), m.p. 140-142ºC. R_f 0.58 (10:1 chloroform-methanol).

Synthesis of compound 3. A mixture of paraphorm (0.005 mol), 2,3-trimethylene-1,2,3,4-tetrahydrohinazalon-4 (0.005 mol) and phosphide acid in dry toluene was stirred for 10 min at room temperature. Then the temperature was raised to reflux for 5H. The reaction was monitored by TLC. After completion of the reaction, toluene was removed by distillation and the residue was purified using column chromatography (5:4, benzene : hexane). Yield of compound 3 is 1.124g (80%), m.p. 167-169ºC. Rf 0.4 (5:4, benzene:hexane).

Synthesis of compound 4. A mixture of m-nitrobenzaldehyde (0.005 mol), 2,3-trimethylene-1,2,3,4-tetrahydrohinazalon-4 (0.005 mol) and phosphide acid in dry toluene was stirred for 10 min at room temperature. Then the temperature was raised to reflux for 5H. the reaction was monitored by TLC. After completion of the reaction, toluene was removed by distillation and the residue was purified using column chromatography (5:4, benzene : hexane). Yield of compound 4 is 1.76 g (87%), m.p. 167-169ºC. R_f 0.52 (5:4, benzene:hexane).

Synthesis of compound 5. A mixture of p-nitrobenzaldehyde (0.01 mol), 2,3-trimethylene-1,2,3,4- tetrahydrohinazalon-4 (0.01 mol) and phosphide acid in dry toluene was stirred for 10 min at room temperature. Then the temperature was raised to reflux for 5H. the reaction was monitored by TLC. After completion of the reaction, toluene was removed by distillation and the residue was purified using column chromatography (5:4, benzene: hexane). Yield of compound 5 is 1.78g (88%), m.p. 167-169ºC. R_f 0.4 (5:4, benzene:hexane).

Conclusions. The new method of preparation of 2,3-threemytilen-1,2,3,4-tetrahydrohinazalon-4 condensation of anthranilic acid with lactam.

Carries out selective renewal of $N_1=C_2$ double bonds of 2,3-thremytilen-1,2,3,4- tetrahydrohinazalon-4. The synthesis of new α-aminophosphonic acid was achieved in high yields through a one-pot three- component reaction process, a Kabachnik-Filds reaction. It involves the reactions among 2,3-trimethylene-1,2,3,4- tetrahydrohinazalon-4, substituted aromatic aldehydes, and phosphorous acid in dry toluene at reflux temperature. Their structures were determined by elemental analysis IR, 1H-NMR, and mass spectral data.

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