Cyclocondensation of 2-aryl aminomethylene-3-aminoquinazolin-4-one with some acids derivatives and formic acid. Applications to the synthesis of some 3,4-dihydro-1,2,4-triazino[6,1-b]quinazolin-4-one derivatives

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Abstract

Ethyl N-(N`-aryl glycinyl) anthranilate (1,2) have been prepared by the reaction of ethyl anthranilate with N-aryl glycinyl chloride. The synthesized compounds (1,2) were allowed to react with hydrazine hydrate in n-butanol to afford 2-substituted -3- aminoquinazolin-4-one (3,4). Compounds (3,4) were reacted with some acids derivatives (acetic anhydride, triflouroacetic anhydride, benzoyl chloride and dimethyl carbonate) and formic acid, to give 3,4- dihydro-1,2,4-triazino [6,1-b] quinazolin -4- one derivatives (5-14). The identification of the synthesized compounds were carried out by IR spectroscopy as well as melting points.

Keywords: Cyclocondensation, 3- aminoquinazolin -4- one, 1,2,4-triazino [6,1-b] quinazolin-4-one

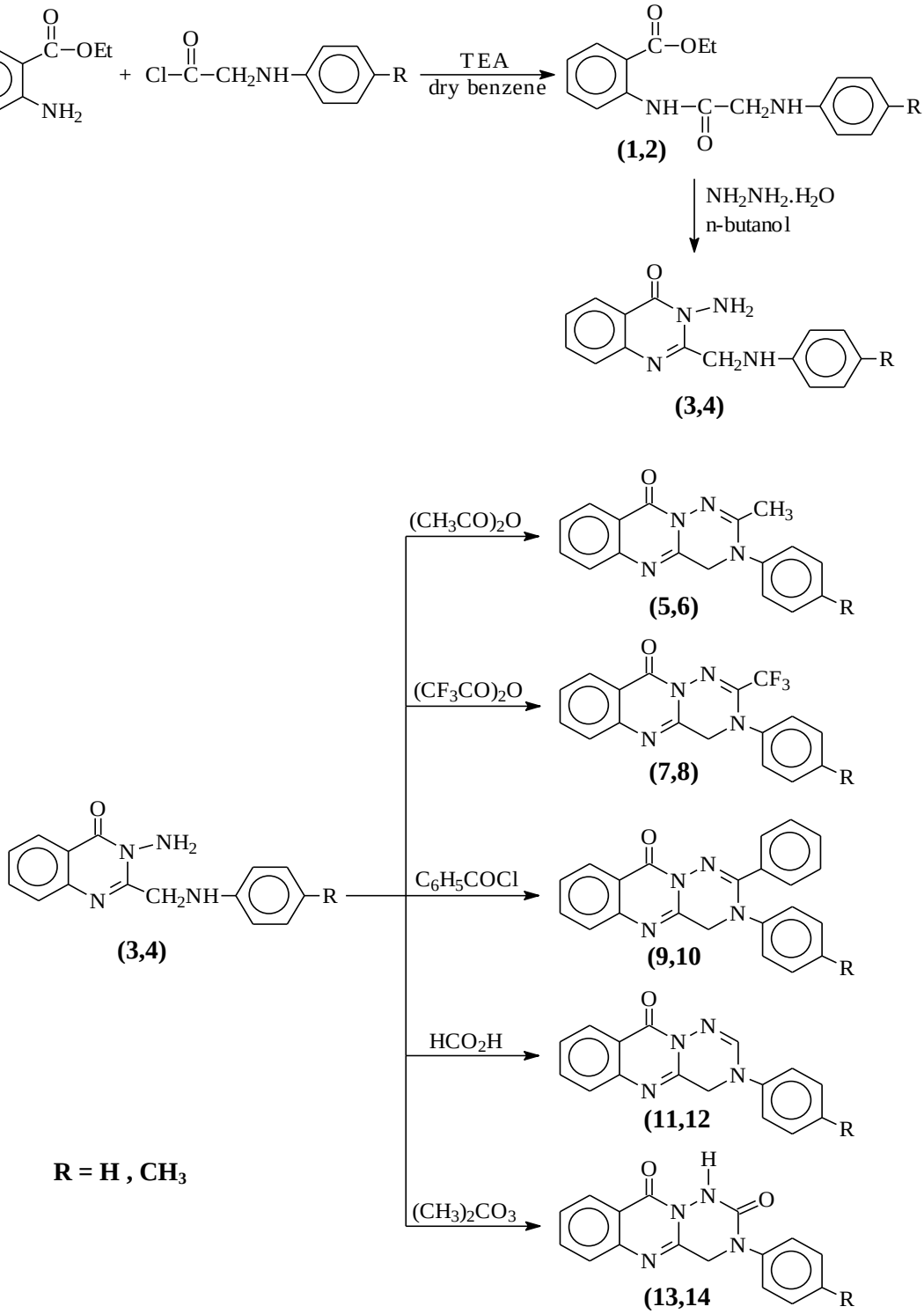
Introduction

4-Quinazolinones are biologically interesting compounds, and were known to possess various biological activities, such as antimicrobial, antiparkinson, traumatic brain treatment and as muscle relaxants[1,2]. Their chemistry has received considerable attention[3-5].

One of the most important features in 4-quinazolinones chemistry is their use as key starting materials for further transformations[6]. They are indeed useful intermediates in organic synthesis affording through reaction with some other materials fused heterocyles[7]. Moreover, the biological activity of fused quinazolinones has led to intensive research on their synthesis[6,7].

From literatures review we found out numerous methods for 4-quinazolin-4-ones synthesis. One of the most famous route, was the condensation of benzoxazinones with different nitrogen nucleophiles, which carried out through heteroring opening followed by ring closure[8,9]. Also, these compounds could be achieved by treating anthranilic acid with alkyl isothiocyanate[10].

In the present study, 3-aminoquinazolin-4-ones were prepared depending on the procedure described in Mkrtchyan *et al*. (2002)[11], which includes the reaction of amido ester with hydrazine hydrate in n-butanol. Despite the satisfactory biological activity of quinazolinones, we found it is of interest to try improving this activity by deriving new fused heterocyles out of 3-aminoquinazolin-4-ones. Scheme (1) illustrates the gathered preparation steps which have been carried out in this work.



Scheme (I)

Experimental

All chemicals were purchased from Fluka and BDH Chemical Ltd. The melting points were measured on an Electrothermal 9300 Engineering LTD and were uncorrected. IR spectra were recorded on Infrared Spectrophotometer Model Tensor 27, Bruker Co., Germany, using KBr discs.

N-Aryl glycine compounds were synthesized according to the procedure described in Abdulmalic (2000)[12]; Parrasion and Brieux (1963)[13]. Ar = Ph: m.p. = 126-127 °C, Lit. = 125-127 °C; Ar = p-$CH_3C_6H_4$: m.p. = 116-118 °C, Lit. = 116-118 °C. N-Aryl glycine chloride had been synthesized and used freshly.

Melting points, yields and IR spectral data of synthesi zed compounds are tabulated in Table 1.

Preparation of ethyl N-(N`-aryl glycinyl) anthranilate (1,2)

Dry triethylamine (TEA) (0.01 mole, 1 g) was added to a solution of ethyl anthranilate (0.01 mole, 1.65 g) in dry benzene (30 ml), and then the corresponding acid chloride (0.01 mole) was added dropwise with continuous stirring. The mixture was refluxed for (4 hrs), and the solvent was evaporated. The residue was collected, washed with water and methanol, and recrystallized from ethanol, (Table 1).

Preparation of 2-aryl aminomethylene-3-aminoquinazolin-4-one (3,4)

A mixture of (0.01 mole) of compounds (1 or 2) and (10 ml) of hydrazine hydrate (85%) in (15 ml) n-butanol was refluxed overnight. The crystals which formed on cooling were filtered off, washed with ethanol and water, dried and recrystallized from ethanol, (Table 1).

Preparation of 2-substituted-3-aryl-3,4-dihydro[1,2,4]triazino[6,1-b] quinazolin-10-one (5-8, 11,12)

A mixture of compounds (3 or 4) (0.01 mole) in (10 ml) of (acetic anhydride or triflouroacetic anhydride or formic acid) was refluxed for (3 hrs). Then, the reaction mixture was cooled and the precipitate was filtered, washed with water and recrystallized from ethanol, (Table 1).

Preparation of compounds (9,10)

Compound (3 or 4) (0.01 mole) was dissolved in dry benzene (30 ml), to this solution, dry triethylamine (TEA) (0.01 mole, 1 g) was added. Then (0.01 mole, 1.4 g) of benzoyl chloride was added dropwise with continues stirring, after the addition had been finished, the mixture was refluxed for (3 hrs). Then the reaction mixture was cooled and poured onto crushed ice, the precipitate was filtered off, washed with cold water and recrystallized from ethanol, (Table 1).

Preparation of compounds (13,14)

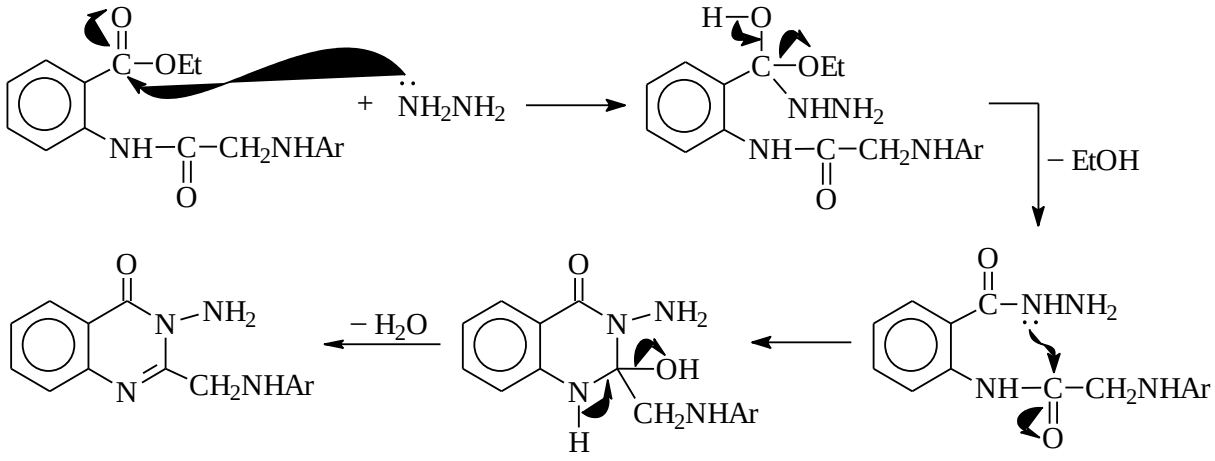
A mixture of (0.01 mole) of compound (3 or 4) and dimethyl carbonate (0.01 mole, 0.9 ml) in (20 ml) of absolute ethanol was refluxed for (2 hrs). The solvent was evaporated under reduced pressure and the crude product was collected and recrystallized from (1:1) water-ethanol, (Table 1).

Results And Discussion

In the present study, of ten of 2-substituted-3-aryl-3,4-dihydro[1,2,4]triazino [6,1-b]quinazolin-10-one via the cyclocondensation of 2-substituted-3-aminoquinazolin-4-one have been synthesized. Ethyl anthranilate was reacted with N-aryl glycinyl chlorides (prepared and reacted immediately) to give ethyl N-(N`-aryl glycyl) anthranilate (1,2). The reaction proceeds through tetrahedral mechanism.

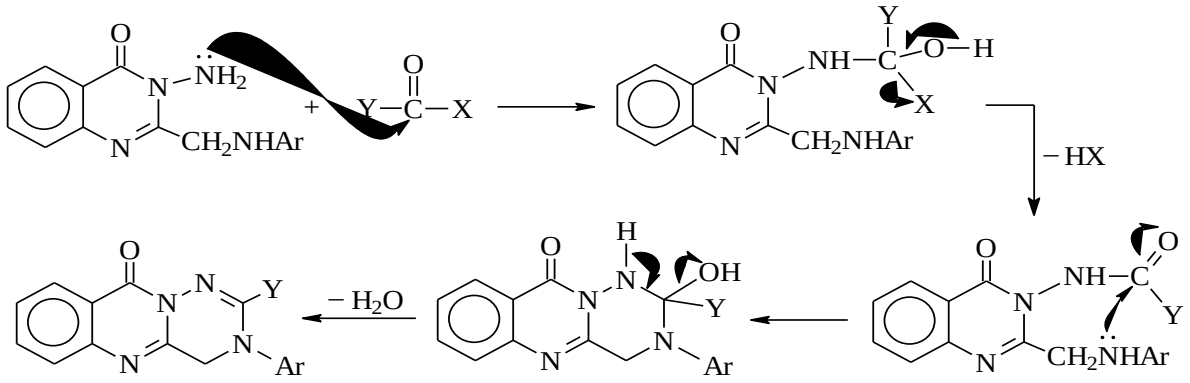
IR spectra of compounds (1,2) showed absorption bands at (3366, 3421 cm^{-1}) due to (νN-H). Also, the spectra gave two strong bands for every compound (1721, 1683; 1730, 1701 cm^{-1}), due to (νC=O ester), whereas the low ones to (νC=O amide) respectively.

The cyclization of compounds (1,2) with hydrazine hydrate was performed by heating compounds (1,2) with an excess of neat hydrazine hydrate to afford 2-aryl aminomethylene-3-aminoquinazolin-4-one (3,4). The expected cyclization mechanism can be illustrated as following:



The structure of compounds (3,4) were confirmed by IR spectra, which gave bands at (3421, 3326 cm^{-1}) due to (□N-H), (1716, 1695 cm^{-1}) related to C=O and bands at (1647, 1653 cm^{-1}) which related to (□C=N), besides other bands given in Table (2).

The synthesized compounds (3,4) were then used in cyclocondensation reaction. When they reacted with acetic anhydride, triflouroacetic anhydride and benzoyl chloride, 2-substituted – 3 – ary l - 3, 4-dihydro [1, 2, 4] triazino [6,1-b] quinazolin – 10 - one compounds (5 - 10) were produced, respectively. Compounds (11,12) were prepared by the same previous manner with the difference of giving products with no substituents on position 2 of fused heterosystem. The mechanism of these reactions could be visualized in the following steps:

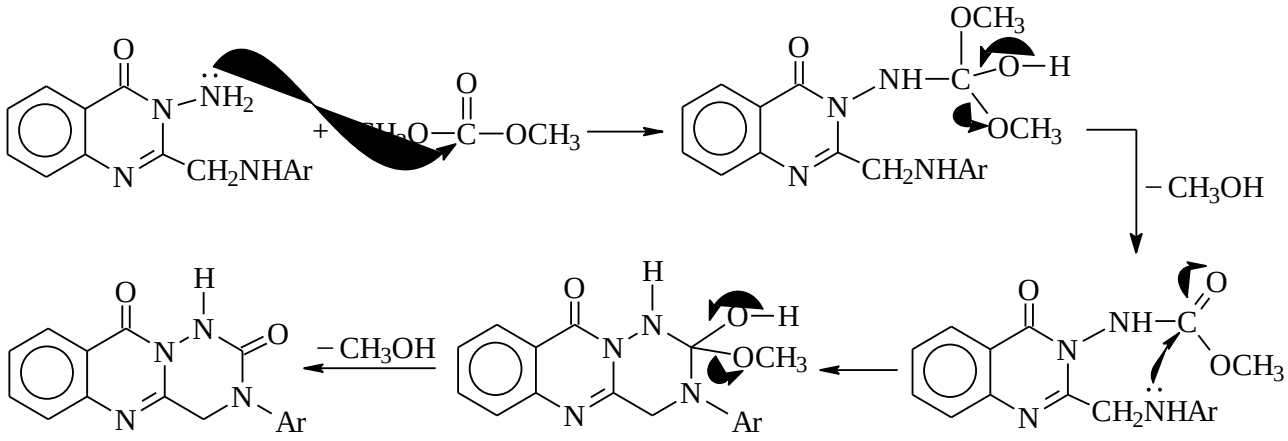


X = CH_3COO , Y = CH_3 → (5,6)

X = CF_3COO , Y = CF_3 → (7,8)

IR spectra of compounds (5-12) showed absorption bands at (1671-1705 cm^{-1}) due to (□C=N). The interesting fact was that the spectra did not give any bands for (□N-H). As a matter of fact, that enhances the idea of that the reaction had given the compounds (5-12) with suggested structures (Scheme I).

Finally, compounds (3,4) were reacted with dimethyl carbonate to give the desired compounds (13,14). The suggested mechanism for this reaction passes through the same steps that mentioned before for the synthesis of compounds (5-12), which can be shown as following:



IR spectra of compounds (13,14) gave bands at (3334,3323cm^{-1}) and (1630,1615cm^{-1}) due to (□N-H and □C=N) respectively, besides other bands reported in Table (1). Moreover, the spectra gave broad bands at(1673,1671cm^{-1}), that shape of these bands related to the interference of two stretching bands of C=O amide.

Table (1): Physical and IR spectral data of (1-14)

Comp. No.	Yield %	m.p. °C	IR ν (cm^{-1}) KBr				
			N-H	C-H aliphatic	C=O	C=N	C┈┈C Ar
1	73	175-177	3366	2947	1683,1721	-	1594
2	64	147-148	3421	2952	1701,1730	-	1541
3	82	86-88	3421	2933	1716	1647	1541
4	77	210-212	3326	2945	1695	1657	1555
5	81	140-142	-	2929	1705	1634	1595
6	69	198-200	-	2925	1703	1644	1607
7	70	82-84	-	2928	1699	1650	1605
8	78	75-77	-	2957	1700	1665	1608
9	72	163-165	-	2932	1671	1641	1595
10	62	Oily	-	2923	1684	1630	1603
11	68	179-181	-	2918	1682	1632	1593
12	83	178-180	-	2922	1683	1641	1600
13	58	Oily	3334	2936	1673	1630	1594
14	84	58-60	3323	2920	1671	1615	1584

References

1. M.E. Abdel-Fattah, E.A. Soliman and S.M.A. Soliman, Synthesis and reactions of 2 - [2 - (2, 4,6 - trimethyl benzoyl) vinyl] - 4H -3,1- benzoxazin – 4 - one and antimicrobial activity. Indian J. Heterocycl. Chem., 8 (3) (1999) 177-182.
2. A. Dandia, S. Sanan, S. Bhagat and K. Arya, Synthesis of some bioactive heterocycles: Investigation of the reactions of indole-2,3-dione derivatives with 2,3-diamino-4 (3H)-quinazolone, 2001 (Internet).
3. B.L. Chenard and K.D. Shenk, Methods of preparing substituted 3-phenyl-and 3-pyridyl-4(3H)-quinazolinones and atropisomers there of, useful as AMPA inhibitors or their intermediates, Eur. Pat. Appl. EP 934,934 (Cl.C07D239/91), 11 Aug. 1999, Chem. Abstr., 131 (1999) 11, 1999, 144610v.
4. S.S. Tiwari and R.K. Satsangi, Possible antiparkinson compounds: Part I. Synthesis of some 2-aryl-3-(1,3,4-thiadiazol – 2 – yl) – quinazolin – 4 (3H) - ones, J. Indian Chem. Soc., LV (1978) 477-478.
5. O. Mathieson, 3-Phenyl quinazolones, French Patent, 1964, 1367788; Chem. Abstr., 1965, 62 (1964) 1672a.
6. H.M.F. Madkour, Reactivity of 4H-3,1-benzoxazin-4-ones towards nitrogen and carbon nucleophilic reagents: applications to the synthesis of new heterocyles, ARKAT USA, 1-8 (2006).
7. M.E.A. Zaki, Synthesis of novel fused heterocycles based on pyrano[2,3-c]pyrazole, Molecules, 3 (1998) 71-79.
8. H.A. Basheer, M.A. Abdulmalic and N.S. Ezzat, Synthesis of some tetrahydro-benzoxazine and tetrahydroquinazoline derivatives, Raf. Jour. Sci., 15 (2) (2004) 29-35.
9. S.S. Tiwari V.K. Pandey, Synthesis of possible antiparkinsonian compounds. Part X: Synthesis of 2,6,8-trisubstituted benzoxazinones and their corresponding 3-hydroxy-quinazolinones, J. Indian Chem. Soc., LII (1975) 736-737.
10. J.F. Bereznak, Z.Y. Chang, T.P. Selby and C.G. Sternberg, Preparation of quinazolinones as agrochemical fungicides, U.S. US 5,945,423 (1998) (Cl.514-259; C07D239/72); Chem. Abstr., Vol. 131, No. 13, 1999, 170360h.
11. A.P. Mkrtchyan, A.S. Noravyan and V.M. Petrosyan, Derivatives of condensed thieno[2,3-d]pyrimidines. 15*. Synthesis of 2-substituted 3-amino-6,6-dimethyl-5,6-dihydro-8H-pyrano[4`,3`:4,5]-thieno[2,3-d]pyrimidin-4-ones, Chemistry of Heterocyclic Compounds, 38 (2) (2002) 238-241.
12. M.A. Abdulmalic, Synthesis and study of some substituted biologically active oxadiazole, thiadiazole and triazole, M.Sc. Thesis, University of Mosul, 2000.
13. S. Parrasion and G.A. Brieux, Ultraviolet absorption spectra of N - aryl glycine and derivatives, Bull. Soc. Chim. France, 35 (1963); Chem. Abstr., 1963, 58, 13305e.

الحولقة التكثيفية لـ ٢- اريل امينو مثيلين -٣- امينو كوينازولين -٤- اون مع بعض مشتقات الحوامض العضوية وحامض الفورميك. تطبيقات في تحضير عدد من معوضات ٤،٣- ثنائي هايدرو-٤،٢،١- ترايازوينو[6,1-b] كوينازولين-٤- اون

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الملخص

تم تحضير N- (`N- اريل كلايسيل) انثرانيلات الاثيل (٢،١) من خلال تفاعل انثرانيلات الاثيل مع N- اريل كلوريد الكلايسينيل، ثم سمح للمركبين المحضرين بالتفاعل مع الهيدرازين المائي في ن – بيوتانول ليعطي ٢- معوض-٣- امينو كوينازولين-٤- اون (٤،٣). تم مفاعلة المركبين (٤،٣) مع عدد من مشتقات الحوامض العضوية (انهيدريد الخليك وثلاثي فلورو انهيدريد الخليك وكلوريد البنزويل وكاربونات ثنائي المثيل) وحامض الفورميك، لتعطي مشتقات ٤،٣- ثنائي هيدرو-٤،٢،١- ترايازينو[6,1-b] كوينازولين -٤- اون (٥-١٤). تم تشخيص المركبات المحضرة باستخدام طيف الاشعة تحت الحمراء بالاضافة الى درجات الانصهار