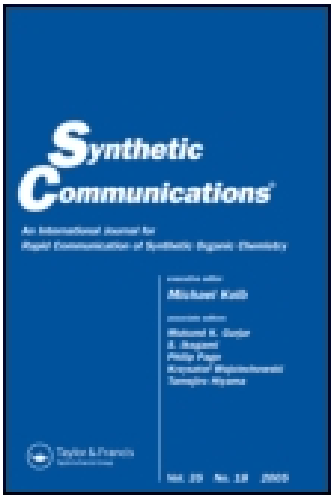

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

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Novel Four-Step Synthesis of Thioxo-quinazolino[3,4-a]quinazolinone Derivatives

Behnaz Shafii [a], Mina Saeedi [a], Mohammad Mahdavi [a], Alireza Foroumadi [a] & Abbas Shafiee [a]

[a] Department of Medicinal Chemistry, Faculty of Pharmacy and Pharmaceutical Sciences Research Center, Tehran University of Medical Sciences, Tehran, Iran

Accepted author version posted online: 27 Aug 2013.Published online: 29 Oct 2013.

To cite this article: Behnaz Shafii, Mina Saeedi, Mohammad Mahdavi, Alireza Foroumadi & Abbas Shafiee (2014) Novel Four-Step Synthesis of Thioxo-quinazolino[3,4-a]quinazolinone Derivatives, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 44:2, 215-221, DOI: 10.1080/00397911.2013.800211

To link to this article: http://dx.doi.org/10.1080/00397911.2013.800211

Synthetic Communications®, 44: 215–221, 2014

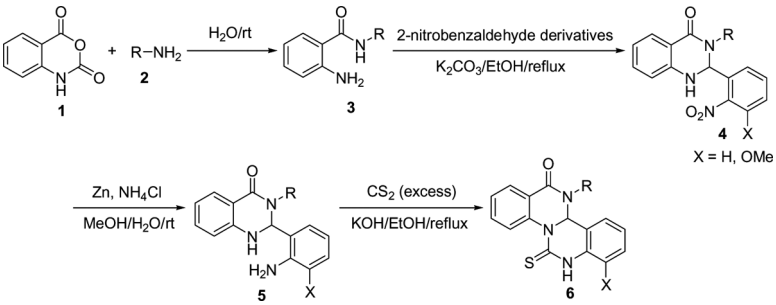
ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397911.2013.800211

NOVEL FOUR-STEP SYNTHESIS OF THIOXO-QUINAZOLINO[3,4-*a*]QUINAZOLINONE DERIVATIVES

Behnaz Shafii, Mina Saeedi, Mohammad Mahdavi, Alireza Foroumadi, and Abbas Shafiee

Department of Medicinal Chemistry, Faculty of Pharmacy and Pharmaceutical Sciences Research Center, Tehran University of Medical Sciences, Tehran, Iran

GRAPHICAL ABSTRACT



Abstract *A novel synthesis of thioxo-quinazolino[3,4-a]quinazolinone framework was developed through a four-step reaction starting from isatoic anhydride. The resulting 2-aminobenzamides from the reaction of isatoic anhydride and different amines underwent coupling–cyclization reaction with 2-nitrobenzaldehydes, reduction of nitro group, and then cyclization reaction with carbon disulfide (CS_2). All steps were carried out under easy and user-friendly conditions in a short time without using expensive catalysts or reagents.*

[Supplementary materials are available for this article. Go to the publisher's online edition of Synthetic Communications® *for the following free supplemental resource(s): Full experimental and spectral details.]*

Keywords Carbon disulfide (CS_2); heterocycles; 2-nitrobenzaldehydes; thioxo-quinazolino[3,4-*a*]quinazolinone

INTRODUCTION

The prominence of the quinazoline unit in various medicinal organic compounds has been the subject of great interest because of its medicinal and distinguished biological activities.[1] The quinazolinone and quinazolinthione

Received March 5, 2013.

Address correspondence to Abbas Shafiee, Department of Medicinal Chemistry, Faculty of Pharmacy and Pharmaceutical Sciences Research Center, Tehran University of Medical Sciences, Tehran 14176, Iran. E-mail: ashafiee@ams.ac.ir

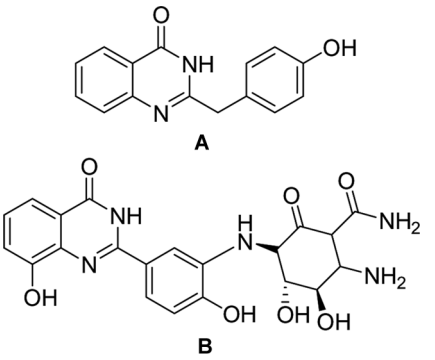
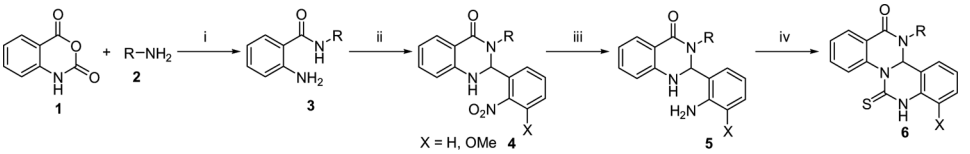


Figure 1. Structure of isolated 2-(4-hydroxybenzyl)quinazolin-4(3*H*)-one **A** and farinamycin **B** from *Cordyceps*-colonizing fungus *Isaria farinose* and *Streptomyces griseus*, respectively.

(thioxo-quinazolinone) moieties are well known for their anticonvulsant,[2] antihypertensive,[3] anti-inflammatory,[4] and phosphodiesterase inhibitor[5] properties. Recently, Corbett et al. showed that fused quinazolines were HIV-1 non-nucleoside reverse transcriptase inhibitors.[6] More to the point, the quinazolinone nucleus can be found in natural products such as 2-(4-hydroxybenzyl)quinazolin-4(3*H*)-one (Fig. 1, **A**) obtained from cultures of the *Cordyceps*-colonizing fungus *Isaria farinosa*[7] and farinamycin (Figure 1, **B**), a quinazoline metabolite isolated from *Streptomyces griseus*.[8]

Unfortunately, the biological and medical activities of the quinazolinthiones have not been fully investigated yet. Recently, Bahekar et al. investigated quinazolinthione derivatives and found that they showed bronchodilator activity using in vitro and in vivo methods (standard animal models).[9] In addition, El Azab et al. described the synthesis of novel quinazolinone and quinazolinethione derivatives that showed potential as antitumor agents.[10] A literature review revealed that quinazolinethione has been center of attention not only for the biological properties but also they have been suitable intermediates for the preparation of useful bioactive compounds.[11]

As part of our ongoing research program pertaining to the synthesis and design of new heterocyclic compounds,[12–14] we have devised a novel synthetic scheme to obtain fused thioxo-quinazolino[3,4-*a*]quinazolinones, and we realized that their synthesis and biological activities were not fully understood. Thus, we tried to present a suitable protocol for the synthesis of this class of heterocycles and thioxo-quinazolino[3,4-*a*]quinazolinone derivatives (Scheme 1).



Scheme 1. Synthesis of fused thioxo-quinazolino[3,4-*a*]quinazolinones **6**: (i) in water at room temperature (2–3 h); (ii) 2-nitrobenzaldehyde or 3-methoxy-2-nitrobenzaldehyde, K_2CO_3/EtOH at reflux (2–4 h); (iii) Zn, NH_4Cl, MeOH, water at room temperature (1–2 h); (iv) CS_2 (excess), KOH/EtOH at reflux (3–5 h).

RESULTS AND DISCUSSION

We recently reported synthesis of diverse new heterocyclic compounds starting from isatoic anhydride.[12,15] Because of the good results and easy procedure, we were encouraged to design a novel strategy for the synthesis of quinazolino[3,4-*a*] quinazolinones utilizing isatoic anhydride. For this purpose, we outlined a synthetic route in four steps for the preparation of these compounds (Scheme 1).

The first step of our synthetic route included preparation of various 2-aminobenzamide derivatives **3** from the reaction of isatoic anhydride **1** and various amines **2** in water at room temperature.[12,15] Clearly the reaction is conducted by the nucleophilic attack of amine on the isatoic anhydride with liberation of CO_2.[16]

The second step of our synthetic scheme was preparing the 2,3-dihydro-2-(2-nitrophenyl)-3-arylquinazolin-4(1*H*)-one derivatives **4**. A literature survey shows that there are various procedures for the one-pot, three-component synthesis of quinazolin-4(1*H*)-ones starting from isatoic anhydride, amines, and aldehydes.[17] We investigated some of these procedures and obtained the related products **4** in poor yields. It seems that those methods did not work as efficiently as we expected for the selected sterically hindered aldeydes in our study. Also some of them used complex or expensive catalysts.[18] We observed that heating mixture of a stoichiometric amount of 2-aminobenzamides **3**, 2-nitobenzaldehyde derivatives, and potassium carbonate (K_2CO_3) in EtOH led to the formation of compounds **4** in good yields.

In the third step, reduction of nitro group in compounds **4** gave 2-(2-aminophenyl)-2,3-dihydro-3-arylquinazolin-4(1*H*)-ones **5**. It should be noted that the best reaction conditions for reduction of the NO_2 group was obtained using a mixture of Zn powder and ammonium chloride (NH_4Cl) in $MeOH/H_2O$, at room temperature.

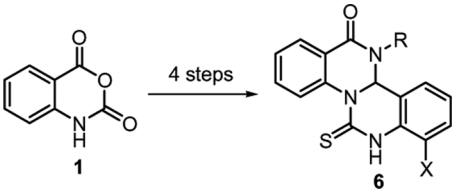
In the fourth step, the final products **6** were obtained easily by heating the mixture of compounds **5** and an excess amount of carbon disulfide (CS_2) in the presence of potassium hydroxide (KOH).

The structure of all products was confirmed on the basis of their mass spectroscopic fragmentation pattern analysis and ^1H and ^{13}C NMR spectra. For instance, for 12-benzyl-6-thioxo-11b,12-dihydro-6*H*-quinazolino[3,4-*a*]quinazolin-13(7*H*)-one **6a** (Table 1, entry 1), the MS peak (m/z 371) associated with the molecular ion was observed and was in accordance with calculated mass for $C_{22}H_{17}N_3OS$. The MS shows a strong peak (m/z 237) that is related to elimination of the benzyl and CS groups and the formation of 2-(2-aminophenyl)quinazolin-4(1*H*)-one. Also a rather strong peak was also observed (m/z 266) resulting from the loss of phenylmethanimine.

^1H NMR spectrum of **6a** consisted of two doublet signals at 4.06 and 4.81 for the two protons of NCH_2 and a singlet at 6.67 ppm for CH. The 13 protons associated with the aromatic rings were observed around 6.71–8.01 ppm. The singlet signal at 11.61 corresponded to the NH group. As expected, the ^{13}C spectrum exhibited 20 distinct resonances. Two signals at 44.0 and 68.6 are related to two aliphatic carbons. Sixteen signals related to aromatic carbons were observed around 113.0–142.5. Two signals at 162.9 and 175.4 ppm are related to C=O and C=S, respectively.

As can be seen in Table 1, we could synthesize various thioxo-quinazolino[3,4-*a*]quinazolinone derivatives through the described method. It is worth mentioning that all 2-aminobenzamides showed good reactivity toward 2-nitrobenzaldehydes

Table 1. Synthesis of fused thioxo-quinazolino[3,4-*a*]quinazolinone derivatives **6**



Entry	R	X	Product **6**	Yield (%)[a]
1	$C_6H_5CH_2$-	H	**6a**	88
2	$C_6H_5CH_2$-	OMe	**6b**	80
3	4-Me-$C_6H_4CH_2$-	H	**6c**	82
4	4-Me-$C_6H_4CH_2$-	OMe	**6d**	79
5	4-F-$C_6H_4CH_2$-	H	**6e**	80
6	4-F-$C_6H_4CH_2$-	OMe	**6f**	80
7	2-Cl-$C_6H_4CH_2$-	H	**6g**	81
8	Furfuryl	H	**6h**	75
9	CH_2=$CHCH_2$-	H	**6i**	84
10	$CH_3CH_2CH_2$-	H	**6j**	81

[a]Isolated yields.

and all of corresponding products tolerated reduction reaction and also cyclization reaction with CS_2. It should be noted that different electron-donating and electron-withdrawing substituents on either *para* or *ortho* positions of aromatic rings did not show remarkable differences in the yield of products and reaction times. In the case of products **6h**, lower yield can be related to electron-withdrawing effect of furfuryl, which decreased the nucleophilicity of NH_2 group of furfurylamine and also NH in 2-amino-*N*-((furan-2-yl)methyl)benzamide.

CONCLUSION

In summary, we have developed a novel and efficient four-step synthesis of fused thioxo-quinazolino[3,4-*a*]quinazolinone derivatives starting from isatoic anhydride as an available starting material, in moderate to good yields. All four steps included easy and user friendly procedures which did not diminish yields of products significantly. All steps were done without using expensive catalyst and reagents in short time. Noticing that synthesis and biological evaluation of the title compounds have not been investigated, we hope that the described strategy for the synthesis of these potentially bioactive products can open a new horizon for organic and medicinal chemists. These compounds may possess cytotoxic activities.

EXPERIMENTAL

Melting points were taken on a Kofler hot-stage apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker FT-500, using tetramethylsilane (TMS) as an internal standard. The infrared (IR) spectra were obtained on a Nicolet Magna FTIR 550 spectrophotometer (KBr disks). Mass spectra were recorded on an

Agilent Technology (HP) mass spectrometer operating at an ionization potential of 70 eV. Elemental analyses were carried out with a Perkin-Elmer model 240-C apparatus.

Synthesis of Thioxo-Quinazolino[3,4-*a*]quinazolinone Derivatives 6: General Procedure

A mixture of 2-(2-aminophenyl)-2,3-dihydro-3-arylquinazolin-4(1*H*)-one derivatives **5** (2 mmol), carbon disulfide (CS_2) (5 mmol), and potassium hydroxide (KOH) (2 mmol) in EtOH (10 mL) was heated at reflux for 3–5 h. After completion of the reaction (checked by thin-layer chromatography, TLC), the reaction mixture was cooled down to room temperature and poured into ice-cold water, and the white precipitates were filtered off and recrystallized from EtOH to give pure produts **6**.

12-(4-Fluorobenzyl)-8-methoxy-6-thioxo-11b,12-dihydro-6*H*-quinazolino[3,4-*a*]quinazolin-13(7*H*)-one (6f)

Yield: 0.33 g (80%); white crystal; mp 220–222°C. IR (KBr): 3440, 3152, 3118, 3026, 1648, 1602, 1517, 1430, 1180 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): $\delta = 3.80$ (s, 3 H, OMe), 4.02 (d, $J = 15.9$ Hz, 1 H, benzylic), 4.84 (d, $J = 15.9$ Hz, 1 H, benzylic), 6.65 (s, 1 H, CH), 6.70–6.73 (m, 2 H, H_9, H_{10}), 6.92–6.96 (m, 3 H, H_{11}, $H_{3'}$, $H_{5'}$), 7.09–7.16 (m, 2 H, $H_{2'}$, $H_{6'}$), 7.51 (t, $J = 8.0$ Hz, 1 H, H_2), 7.63 (dt, $J = 8.0$, 1.1 Hz, 1 H), 7.68 (d, $J = 8.0$ Hz, 1 H, H_4), 8.00 (dd, $J = 8.0$, 1.1 Hz, 1 H, H_1), 10.00 (s, 1 H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 43.4$, 56.2, 68.6, 113.1, 114.1, 114.6 (d, $J_{C\text{-}F} = 21.2$ Hz), 120.5, 124.1, 124.3, 126.0, 127.1, 127.3, 127.5, 127.9 (d, $J_{C\text{-}F} = 7.8$ Hz), 130.9, 133.8, 142.6, 144.9, 160.9 (d, $J_{C\text{-}F} = 240.7$ Hz), 162.9, 175.6. MS: m/z (%) = 419 (35) $[M]^{+\cdot}$, 296 (100), 267 (49), 253 (40), 237 (31), 162 (23), 134 (12), 109 (66), 77 (18). Anal. calcd. for $C_{23}H_{18}FN_3O_2S$: C, 65.86; H, 4.33; N, 10.02. Found: C, 65.59; H, 4.55; N, 9.86.

SUPPORTING INFORMATION

Full experimental details and ^1H and ^{13}C NMR spectra are available. This material can be found via the Supplementary Content section of this article's Web page.

ACKNOWLEDGMENTS

This research was supported by grants from the research council of Tehran University of Medical Sciences, Iran National Science Foundation (INSF), and Iran National Elite Foundation (INEF).

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