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One-pot, Simple, and Convenient Synthesis of 2-Thioxo-2,3-dihydroquinazolin-4(1*H*)-ones

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Summary. A simple and convenient method for the synthesis of diverse 2-thioxo-2,3-dihydroquinazolin-4(1*H*)-ones was developed as one-pot reaction of anthranilic acid esters, primary amines, and bis(benzotriazolyl)methanethione in presence of the amidine base *DBU*.

Keywords. Amines; Benzotriazole; Cyclization; *DBU*; Thioxoquinazolinones.

Introduction

The synthesis of thioxoquinazolinone heterocycles has become the cornerstone for synthetic chemists and gained extensive importance in medicinal chemistry because of their diverse pharmacological activities including antimycobacterial [1a–d], antifungal [1e], antimalarial [1f], antihypertensive [2a–c], antihistaminic [2d–i], local anesthetic [3a], anti-*Parkinson* [3b], cardiotonic [3c], anticancer [3d], antiviral [3e–g], and thymidylate synthase inhibitory activities [3h, i]. Several simple and condensed quinazolines are also known to exhibit potent CNS activities as analgesic [4a–c], anti-inflammatory [4d–f], and anti-convulsant activities [4g, h]. Besides these, the quinazolinone skeleton is frequently encountered as building block for hundreds of naturally occurring alkaloids [5], and hence the exploration of this skeleton as privileged new chemical entities (NCEs) in drug discovery research is beyond doubt of paramount importance for the synthesis chemist.

The preparative methods leading to these molecules include the reaction of (i) substituted anthranilic acids or its functional derivatives with isothiocyanates [6a, b], thioureas [6c], excess of refluxing formamide [6d], imidates [6e], methyl *N*-aryldithiocarbamates [6f, g], ammonium aryldithiocarbamates [6h, i], amine and CS_2 in basic medium [6j], *R*NHCOO*Et* and imidazole [6k], amine and sodium cyanate, $CSCl_2$ either in presence of N*Et*$_3$ [6l] or hydrazine [6m], polymer supported $FeCl_3$, orthoesters, and amines under solvent free conditions [6m], (ii) isothiocyanates either with dimethylsulfoxonium-2-(methylamino)benzoylmethylide [7a] or in refluxing *N*-methylanthranilonitrile followed by hydrolysis [7b], (iii) urethanes either with aniline or with acetanilides [7c], (iv) anthranilamides with carbonyl compounds [7d, e], (v) *N*-acylanthranilic acids either with amines [7f] or with urethanes [7g], (vi) 1,1′-carbonyldiimidazole and amines [7h, i], (vii) anilines, CS_2, NaOH in *DMSO* followed by treatment with Me_2SO_4 and then alkyl anthranilate in ethanol [2i], (viii) dithiocarbamate, *e.g.* 4-oxo-3*H*-quinazolin-3-yl) dithiocarbamic methyl ester (obtained from anthranilic acid and anhydride) with amines [7j], (ix) oxidation of 2-aminobenzonitrile followed by treatment with acid halides in basic condition [8a], (x) oxidation of 3-arylimino-2-indolinones with peracid [8b], (xi) acidic treatment of 2-(3-phenylthioureido)-

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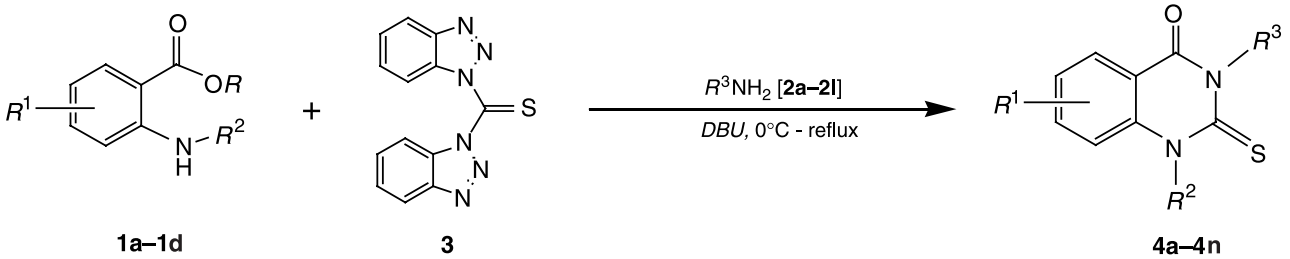
benzoic acid [8c], (xii) isotoic anhydride either with isothiocyanate [8d, e], or with amine and isothiocyanates under MW irradiation [8f], (xiii) aza-*Wittig* reactions of *R*-azido imides [8g, h], and (xiv) cyclization of substituted 2-(methylcarboxy)benzeneisothiocyanates either with amines [8i], or amino acids, hydrazines, hydrazides, sulfohydrazides, or thiosemicarbazides [8j]. Through polymer supported synthesis several combinatorial assemblies of quinazolinones and their thioxo derivatives have also been well documented in literature [7h, 9a–i].

Although some of these synthesis methods are very useful, most of them are associated with one or the other limitations, such as involving two or more steps, use of toxic chemicals, *e.g.* thiophosgene, employment of harsh reaction conditions, long reaction times, low reaction yields, and moreover the low availability of starting materials. Due to these facts and reasons, the synthesis of thioxoquinazolines with diverse substitution patterns by a simple, safe, and high yielding methodology has become a field of increasing interest in synthetic and medicinal chemistry during the past few years, and in this fascinating field we wish to report a new, convenient, and good to high yielding one-pot method through benzotriazole mediated strategy.

Results and Discussion

Looking for a very easy and convenient synthesis of thioxoquinazolinones, we turned our attention to bis(benzotriazolyl)methanethione, and decided to check whether it is possible to find a simple and direct one-pot procedure that may be compatible with some other substituents. Very recently we have reported a simple and practical one-pot method for the synthesis of diverse dithiocarbamates using benzotriazole methodology [11]. Benzotriazole not only can easily enter into molecules by a variety of reactions, but can easily be cleaved too after the completion of reaction, and additionally, *Bt*H is cheap and can be recovered and recycled for further use [10]. Therefore we tried to search for an alternate route for the synthesis of heterocycles having thioxoquinazolinone skeleton based on our similar recently reported method [11]. During the course of our studies for the development of biologically active glycoconjugates, *DBU* has been found to be an efficient and mild catalyst [12]. According to our above mentioned experience, we selected organic soluble amidine base *DBU* comprising an excellent balance between reactivity and selectivity. Based on these observations and in continuation of our investigation to search for benzotriazole mediated synthesis methodology, we wish to report a new, simple, and practical one-pot method for the synthesis of thioxoquinazolines with different substitution patterns by the reaction of various primary amines with anthranilic acids or its ester derivatives using the bis(benzotriazolyl)-methanethione (**3**) in presence of *DBU*. The reaction is clean, smooth, and less time consuming, where the desired thioxoquinazolines started to form after 1 h. We tried the reaction with several solvents and found the reaction is good with anhydrous CH_2Cl_2 and *DMF*. To the best of our knowledge this is the first report of benzotriazole mediated and *DBU* catalyzed one-pot synthesis of 2-thioxo-4(3*H*)-quinazolinones. The methodology is convenient, safe, and high yielding with unsubstituted anthranilic acid esters (Scheme 1).

Anthranilic acids or its methyl esters **1a**–**1d** were reacted with different amines **2** (*viz.* benzyl amine, 3-chlorobenzyl amine, aniline, 3-fluoroaniline, 4-chloroaniline, *p*-toludine, *p*-anisidine, cyclohexyl amine, *n*-octyl amine, *n*-dodecyl amine, *etc.*) using bis(benzotriazolyl)methanethione (**3**) and *DBU* in refluxing CH_2Cl_2 for 3 h yielding the desired 2-thioxo-4(1*H*)-quinazolinones (Scheme 1) in good yields (52–89%) as shown in Table 1. Thus, *e.g.* refluxing solution of benzyl amine, bis(benzotria-



1a–1d **3** **4a–4n**

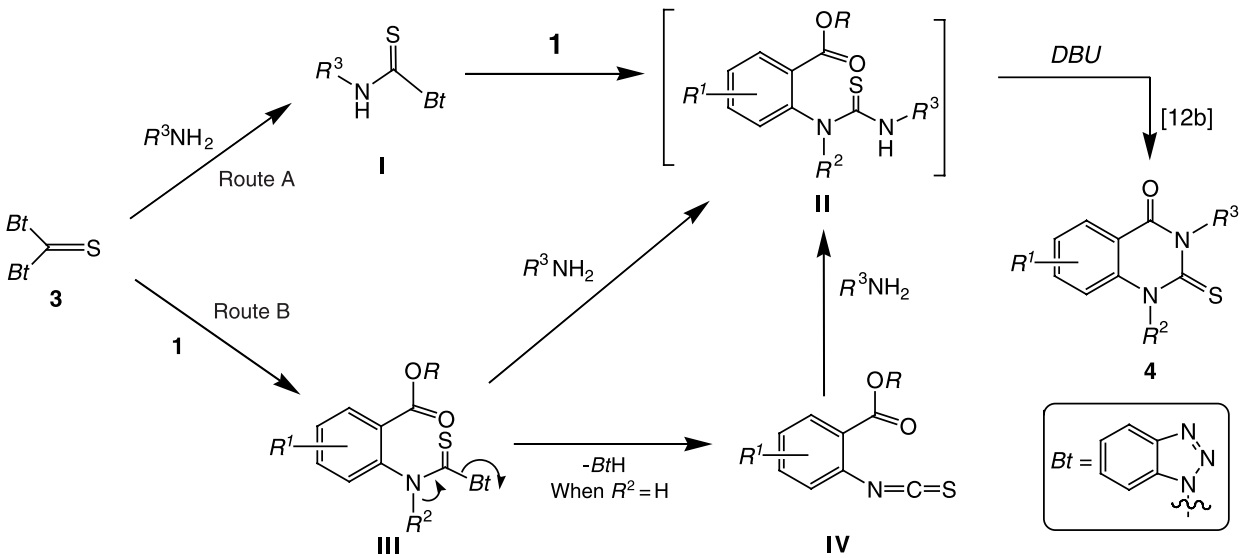
Scheme 1

Table 1. One-pot synthesis of 2-thioxo-2,3-dihydroquinazolin-4(1*H*)-ones **4a**–**4n** with *DBU* as base

Entry	Comp	R^1	R^2	R^3	Time/h	Yield/%
1	**4a**	H	H	$C_6H_5CH_2$	3	89
2	**4b**	H	H	C_6H_5	3	85
3	**4c**	H	H	3-Cl–$C_6H_4CH_2$	3	82
4	**4d**	H	H	3-F–C_6H_4	3	78
4	**4e**	7-chloro	H	3-F–C_6H_4	4	52
5	**4f**	H	H	$CH_3(CH_2)_6CH_2$	3	80
6	**4g**	H	H	$CH_3(CH_2)_{10}CH_2$	3	80
7	**4h**	6,8-dichloro	H	4-COO*Et*–C_6H_4	4.5	54
9	**4i**	H	H	Cyclohexyl	3	72
10	**4j**	H	CH_3	C_6H_5	4	55
11	**4k**	H	CH_3	4-*Me*–C_6H_4	4	55
12	**4l**	H	CH_3	4-O*Me*–C_6H_4	4	54
13	**4m**	H	CH_3	4-Cl–C_6H_4	4	50
14	**4n**	H	CH_3	3-Cl,4-*Me*–C_6H_3	4	52

zolyl)methanethione (**3**) in presence of *DBU* with methyl anthranilate in anhydrous dichloromethane yielded the desired N^3-benzyl-2-thioxo-2,3-dihydro-1*H*-quinazolin-4-one (**4a**) *via* the *Bt*-equivalent isothiocyanate intermediate in good yield (89%). The product was isolated by column chromatography using SiO_2 (20% *Et*O*Ac* in *n*-hexane) and by its spectroscopic data and microanalysis, the structure has been confirmed as cyclic (**4a**), not an open chain thiourea. The reactions with other amines, *e.g.* cyclohexyl amine, *n*-octyl amine, *n*-dodecyl amine, aniline, and substituted anilines were also found to proceed smoothly. However, with methyl substitution on N-1, the reactions proceeded with sluggish rate and afforded the product in comparatively low yield.

In our one-pot addition-cyclation, yields are high particularly with N^1-unsubstituted anthranilic esters; however with N^1-substituted one, *e.g.* N-CH_3, the reaction yield is comparatively low, *i.e.* in general with N^1-unsubstituted derivatives, the cyclization is facile. The reason can easily be understood as depicted in Scheme 1. The mechanism proposed for the reaction involves the addition of amine to **3** *via* route A resulting in the formation of thiocarbamoylbenzotriazoles **I** that on addition of **1** yielded uncyclized thiourea **II**. Route B involves primarily the addition of **1** to **3**, thiocarbamoylbenzotriazoles **III** thus obtained on elimination of *Bt*-H (in case of N^1 unsubstitution) resulted in isothiocyanates **IV**, which finally on addition of amine afforded the same uncyc-



Scheme 2

lized intermediate **II**. The cyclization of **II** proceeds in a similar reported way [12b], which involves abstraction of a proton from the terminal amido functionality by *DBU* giving a thioureidyl anion that results in thioquinazolinones **4a**–**4n** through cyclative amidation.

In conclusion, we developed a new and useful one-pot synthesis protocol for diverse 2-thioxo-4(3*H*)-quinazolinones (through a benzotriazole methodology) by *DBU* catalyzed addition of anthranilic acid/ester and amines to bis(benzotriazolyl)methanethione. The method is convenient, simple in handling, and good to high yielding. Results are encouraging and are needed to be investigated in an extensive manner to develop the total synthesis of natural products containing the thioxoquinazolinone skeleton.

Experimental

Glassware was dried over an open flame before use in connection with an inert atmosphere (N_2) and solvents were evaporated under reduced pressure. Thin layer chromatography (TLC) was performed using silica gel 60 F-254 plates with I_2 vapors as detecting agents followed by spraying with *Draggendorff* reagent. Silica gel (230–400 mesh) was used for column chromatography. *TMS* (0.0 ppm) was used as an internal standard in ^{1}H NMR. Infrared spectra were recorded as KBr pellets by a Perkin Elemer RX-1 spectrometer. Melting points were determined on a Buchi 535 melting point apparatus. Elemental analyses were performed on a Perkin-Elmer 2400 C, H, N analyzer and results were found to be within $\pm 0.4\%$ of the calculated values.

N^3-Benzyl-2-thioxo-2,3-dihydroquinazolin-4(1H)-one (**4a**, $C_{15}H_{12}N_2OS$)
To 0.45 g bis(benzotriazolyl)methanethione (**3**, 1.61 mmol) dissolved in 20 cm^3 anhydrous CH_2Cl_2, 175 mm^3 benzyl amine (1.61 mmol) were added slowly at 0°C under N_2 atmosphere. The mixture was stirred for 5 min and then 210 mm^3 methyl anthranilate (**1a**, 1.62 mmol) and *DBU* (240 mm^3, 1.60 mmol) were added. After 5 min of stirring the reaction was brought to room temperature and stirred for further 10 min and finally refluxed for 3 h. Progress of the reaction was monitored by *TLC*. The reaction mixture was washed with 5% Na_2CO_3 solution followed by 10 cm^3 distilled H_2O to keep the reaction mixture free from liberated benzotriazole, extracted with 2×75 cm^3 CH_2Cl_2, dried (anhydrous Na_2SO_4), and was concentrated under reduced pressure. The crude mass thus obtained was purified over SiO_2 column using 20% *Et*O*Ac* in *n*-hexane as eluent to afford 0.38 g (89%) **4a** as colorless solid. Mp 248°C; IR (KBr): $\bar{\nu} = 3220.3$ (NH), 1662.2 (C=O), 1205.2 (C=S) cm^{-1}; MS: $m/z = 269$ $[M+H]^+$; ^{1}H NMR (300 MHz, CD_3COCD_3): $\delta = 11.74$ (s, 1H, N*H*), 8.06 (d, $J = 7.5$ Hz, 1H, Ar–*H*), 7.69 (d, $J = 7.5$ Hz, 1H, Ar–*H*), 7.50–7.25 (m, 7H, Ar–*H*), 5.78 (s, 2H, CH_2Ph) ppm.

N^3-Phenyl-2-thioxo-2,3-dihydroquinazolin-4(1H)-one (**4b**, $C_{14}H_{10}N_2OS$)
Yield 85%; mp >260°C; IR (KBr): $\bar{\nu} = 3248.0$ (NH), 1663.3 (C=O), 1529.5, 1196.8 cm^{-1}; MS: $m/z = 255$ $[M+H]^+$; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 11.72$ (s, 1H, N*H*), 8.05 (d, $J = 7.8$ Hz, 1H, Ar–*H*), 7.79 (t, $J = 7.8$ Hz, 1H, Ar–*H*), 7.49–7.31 (m, 7H, Ar–*H*) ppm.

N^3-(3-Fluorophenyl)-2-thioxo-2,3-dihydroquinazolin-4(1H)-one (**4d**, $C_{14}H_9N_2FOS$)
Yield 78%; mp 263°C; IR (KBr): $\bar{\nu} = 3242.2$, 1660.7, 1531.2, 1200.2 cm^{-1}; MS: $m/z = 273$ $[M+H]^+$; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 11.76$ (s, 1H, N*H*), 8.05 (d, $J = 7.8$ Hz, 1H, Ar–*H*), 7.80 (t, $J = 7.8$ Hz, 1H, Ar–*H*), 7.57–7.50 (m, 2H, Ar–*H*), 7.41 (t, $J = 7.5$ Hz, 1H, Ar–*H*), 7.25–7.20 (m, 3H, Ar–*H*) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 136.45$, 131.21, 128.72, 126.34, 125.19, 117.71, 116.23, 116.07, 115.77 ppm.

N^3-(3-Fluorophenyl)-2-thioxo-2,3-dihydro-7-chloroquinazolin-4(1H)-one (**4e**, $C_{14}H_8N_2FClOS$)
Yield 52%; IR (KBr): $\bar{\nu} = 34.54.8$, 1658.1, 1615.5, 1258.4, 1207.7 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 11.75$ (s, 1H, N*H*), 8.00 (d, $J = 7.8$ Hz, 1H, Ar–*H*), 7.50–7.18 (m, 6H, Ar–*H*) ppm.

N^3-n-Octyl-2-thioxo-2,3-dihydroquinazolin-4(1H)-one (**4f**, $C_{16}H_{22}N_2OS$)
Yield 80%; mp 138°C; IR (KBr): $\bar{\nu} = 3448.9$, 2925.8, 2855.3, 1650.9, 1538.6, 1379.1, 1348.4, 1161.1 cm^{-1}; MS: $m/z = 291[M+H]^+$; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 10.10$ (s, 1H, N*H*), 8.13 (d, $J = 7.8$ Hz, 1H, Ar–*H*), 7.65 (t, $J = 7.5$ Hz, 1H, Ar–*H*), 7.32 (t, $J = 7.5$ Hz, 1H, Ar–*H*), 4.50 (t, $J = 7.2$ Hz, 2H, NCH_2), 1.77 (m, 2H, CH_2), 1.25 (m, 10H, $5CH_2$), 0.88 (t, $J = 6.6$ Hz, 3H, CH_3) ppm.

N^3-n-Dodecyl-2-thioxo-2,3-dihydroquinazolin-4(1H)-one (**4g**, $C_{20}H_{30}N_2OS$)
Yield 80%; IR (KBr): $\bar{\nu} = 3440.1$, 2915.2, 2880.7, 1644.2, 1553.2, 1189.1 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 10.11$ (s, 1H, N*H*), 8.13 (d, $J = 7.8$ Hz, 1H, Ar–*H*), 7.66 (t, $J = 7.5$ Hz, 1H, Ar–*H*), 7.33 (t, $J = 7.5$ Hz, 1H, Ar–*H*), 4.51 (t, $J = 7.2$ Hz, 2H, NCH_2), 1.76 (m, 2H, CH_2), 1.30–1.20 (m, 18H, $9CH_2$), 0.88 (t, $J = 6.9$ Hz, 3H, CH_3) ppm.

N^1-Methyl-N^3-phenyl-2-thioxo-2,3-dihydroquinazolin-4(1H)-one (**4j**, $C_{15}H_{12}N_2OS$)
Yield 55%; mp >260°C; MS: $m/z = 269$ $[M+H]^+$; IR (KBr): $\bar{\nu} = 1692.5$, 1608.2, 1480.2, 1384.4, 1209.2 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.09$–7.01 (m, 9H, Ar–H), 3.96 (s, 3H, NCH_3) ppm.

N^1-Methyl-N^3-(4-methylphenyl)-2-thioxo-2,3-dihydroquinazolin-4(1H)-one (**4k**, $C_{16}H_{14}N_2OS$)
Yield 55%; mp 250°C; IR (KBr): $\bar{\nu} = 1695.2$, 1608.1, 1515.4, 1385.2, 1220.6 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.00$–7.90 (m, 8H, *Ar*–*H*), 3.97 (s, 3H, NCH_3), 2.43 (s, 3H, *Ar*CH_3) ppm.

N^1-Methyl-N^3-(4-methoxyphenyl)-2-thioxo-2,3-dihydroquinazolin-4(1H)-one (**4l**, $C_{16}H_{14}N_2O_2S$)
Yield 54%; mp 234°C; IR (KBr): $\bar{\nu} = 1691.4$, 1512.9, 1384.6, 1215.8 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.00$–8.11 (m, 8H, Ar–H), 3.97 (s, 3H, N–CH_3), 3.71 (s, 3H, OCH_3) ppm.

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