SYNTHESIS OF 2-THIOXOQUINAZOLIN-4(1*H*)-ONES IN WATER AT ROOM TEMPERATURE

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Potassium carbonate was found to be an efficient catalyst for synthesis of novel 2-thioxoquinazolin-4(1H)-one derivatives via a one-pot condensation of isatoic anhydride with primary amines and phenyl isothiocyanate in water at room temperature

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INTRODUCTION

Quinazolinones are very important structural units found as the main constituents of several bioactive molecules displaying a wide range of biological and pharmacological activities.[1] Owing to the promised properties of quinazolinones such as anti-inflammatory,[2] antimalarial,[3] antihypertensive,[4] anticonvulsant,[5] anti-HIV,[6] and anti-cancer[7] activities, a plethora of research efforts were rewarded to their synthesis. As a consequence, there are a number of synthetic methods available for preparation of quinazolinones.[8-18]

The most common route resorted for synthesis of 4(3*H*)-quinazolinones involves the amidation of 2-aminobenzoic acid or its derivatives, followed by a oxidative ring closure.[19-22] Other synthetic methods include the cyclization of anthranil amides with aldehydes[23] or ketones or even with acid chlorides under acidic or basic conditions.[24-25] However, most of the reported methods involve multistep processes requiring prolong experimental procedures or toxic reagents for giving poor yields.

Moreover, very few methods are available for the synthesis of 2-thioxoquinazolin-4-ones whilst most of the reported methods were developed for synthesis of quinazolin-2,4(1*H*,3*H*)-diones.[26]

Recently, a base-catalyzed intramolecular nucleophilic cyclization of substituted thioureas in DMF for synthesis of 2-thioxoquinazolin-4-ones was reported.[27] In addition, solid-phase syntheses were developed for preparation of many libraries of 2-thioxoquinazolin-4-one derivatives.[28-30]

EXPERIMENTAL SECTION

Materials, methods and instruments

All the chemicals were obtained from Merck or Fluka without further purifications. Melting points were determined on an Electrothermal 9100 melting point apparatus. Silica gel 60_{F254} plates were used for TLC. IR spectra were measured on a Shimadzu IR-470 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were determined on Bruker 500 DRX AVANCE instrument at 500 and 125 MHz, respectively. The elemental analyses (C, H, N) were obtained from a Carlo ERBA Model EA 1108 analyzer carried out on Perkin-Elmer 240c analyzer. Mass spectra were recorded on a FINNIGAN-MAT 8430 Mass spectrometer operating at an ionization potential of 70 eV.

Typical synthesis of compounds (4a-h)

To a magnetically stirred mixture of isatoic anhydride (2 mmol) in 10 mL of water was added a proper primary amine (2 mmol). When the addition was complete, the mixture retained stirring for additional 2 hours at room temperature. After that time, the mixture became milky and phenyl isothiocyanate (2 mmol) and potassium carbonate (0.1 g) were added to it. The mixture was stirred further for nearly 1 hour at room temperature to complete the reaction. Each time the progress of the reaction was monitored by TLC. At the end of reaction, the mixture was diluted with CH_2Cl_2 and washed with water and the organic layer was dried over $MgSO_4$. Evaporation of the solvent under reduced pressure provided a residue which was purified by column chromatography (using n-hexane:ethylacetate in the ratio of 8:2 as eluents) to afford the desired 2-thioxoquinazolin-4(1*H*)-one products (**4a-h**).

2,3-Dihydro-3-phenyl-2-thioxoquinazolin-4(1H)-one (4a).

White powder, m.p. 307-309 °C; IR: ($\nu_{max/cm}^{-1}$): 3247 (N-H), 3068 (C-H), 1664 (C=O), 1197 (C=S); ^{1}H NMR (500 MHz, DMSO): δ= 7.27-7.96 (m, 9H , Ar), 13.03 (s, 1H, NH); ^{13}C NMR (125 MHz, DMSO): 115.6, 116.1, 124.3,

127.3, 128.0, 128.8, 128.9, 135.5, 139.2, 139.6, 159.7, 176.0 ppm. MS (m/z, %): 254 (M^+). Anal. Calcd. For $C_{14}H_{10}N_2OS$: C, 66.12; H, 3.96; N, 11.02. Found: C, 65.92; H, 3.90; N, 11.13.

3-(4-Chlorobenzyl)-2,3-dihydro-2-thioxoquinazolin-4(1H)-one (4b).

White powder, m.p. 317-319 °C; IR: ($\nu_{max/cm}^{-1}$): 3054 (N-H), 2932 (C-H), 1664 (C=O), 1224 (C=S); ^{1}H NMR (500 MHz, DMSO): δ= 5.06 (s, 2H), 7.16-7.59 (m, 8H , Ar), 12.03 (s, 1H, NH); ^{13}C NMR (125 MHz, DMSO): 43.2, 114.6, 125.3, 127.0, 127.4, 128.2, 133.9, 134.7, 137.2, 142.0, 149.6, 159.7 ppm. MS (m/z, %): 302 (M^+). Anal. Calcd. For $C_{15}H_{11}ClN_2OS$: C, 59.50; H, 3.66; N, 9.25. Found: C, 59.41; H, 3.72; N, 9.19.

7-Chloro-2,3-dihydro-3-phenyl-2-thioxoquinazolin-4(1H)-one, (4c).

White powder, m.p. 324-326 °C; IR: ($\nu_{max/cm}^{-1}$): 3159 (N-H), 3005 (C-H), 1717 (C=O), 1180 (C=S); ^{1}H NMR (500 MHz, DMSO): δ= 7.29-7.90 (m, 8H , Ar), 13.06 (s, 1H, NH); ^{13}C NMR (125 MHz, DMSO): 14.9, 56.6, 115.5, 116.4, 124.5, 125.6, 126.3, 126.9, 127.9, 135.4, 138.8, 140.3, 158.3, 176.5 ppm. MS (m/z, %): 288 (M^+). Anal. Calcd. For $C_{14}H_9ClN_2OS$: C, 58.23; H, 3.14; N, 9.70. Found: C, 58.34; H, 3.17; N, 9.58.

2,3-Dihydro-3-(1-phenylethyl)-2-thioxoquinazolin-4(1H)-one (4d).

White powder, m.p. 264-266 °C; IR: ($\nu_{max/cm}^{-1}$): 3310 (N-H), 3025 (C-H_{arom}), 1666 (C=O), 1198 (C=S); ^{1}H NMR (500 MHz, DMSO): δ=1.85 (d, *J* = 7.1 Hz, 3H), 2.08 (q, *J* = 7.1 Hz, H), 7.18-7.80 (m, 9H , Ar), 12.96 (s, 1H, NH); ^{13}C NMR (125 MHz, DMSO): 31.8, 47.0, 55.5, 112.0, 112.3, 115.5, 115.6, 120.4, 124.5, 127.2, 130.8, 135.4, 139.0, 147.4, 148.7, 159.1, 174.9, ppm. MS (m/z, %): 282 (M^+). Anal. Calcd. For $C_{16}H_{14}N_2OS$: C, 68.06; H, 5.00; N, 9.92. Found:C, 68.12; H, 5.04; N, 9.80.

3-(3,4-Dimethoxyphenethyl)-2,3-dihydro-2-thioxoquinazolin-4(1H)-one (4e).

White powder, m.p. 302-305 °C; IR: ($\nu_{max/cm}^{-1}$): 3180 (N-H), 3040 (C-H), 1686 (C=O), 1145 (C=S); ^{1}H NMR (500 MHz, DMSO): δ= 2.51 (t, *J* = 7.5 Hz, 2H), 3.74 (s, 6H), 4.57 (t, *J* = 7.5 Hz, 2H), 7.79-7.97 (m, 7H , Ar), 13.03 (s, 1H, NH); ^{13}C NMR (125 MHz, DMSO): 158.5, 152.3, 145.4, 138.3, 135.6, 131.4, 128.3, 126.5, 125.5, 124.8, 118.5, 21.0, 13.1, 9.0 ppm. MS (m/z, %): 342 (M^+). Anal. Calcd. For $C_{18}H_{18}N_2O_3S$: C, 63.14; H, 5.30; N, 8.18. Found: C, 63.21; H, 5.36; N, 8.03.

2,3-Dihydro-3-((pyridin-2-yl)methyl)-2-thioxoquinazolin-4(1H)-one, (4f)

White powder, m.p. 294-297 °C; IR: ($\nu_{max/cm}^{-1}$): 3268 (N-H), 3071(C-H), 1664 (C=O), 1171 (C=S); ^{1}H NMR (500 MHz, DMSO): δ= 5.77 (s, 2H), 7.22-8.41 (m, 8H , Ar), 13.04 (s, 1H, NH); ^{13}C NMR (125 MHz, DMSO): 50.0, 115.4, 115.7, 120.6, 121.9, 124.5, 127.3, 135.5, 136.5, 139.2, 148.8, 155.3, 159.4, 175.6 ppm. MS (m/z, %): 269 (M^+). Anal. Calcd. For $C_{14}H_{11}N_3OS$: C, 62.43; H, 4.12; N, 15.60. Found: C, 62.48; H, 4.08; N, 15.56.

3-((Furan-3-yl)methyl)-2,3-dihydro-2-thioxoquinazolin-4(1H)-one, (4g)

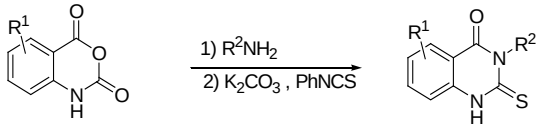
White powder, m.p. 278-280 °C; IR: ($\nu_{max/cm}^{-1}$): 3246 (N-H), 3044 (C-H), 1658 (C=O), 1162 (C=S); ^{1}H NMR (500 MHz, DMSO): δ= 5.65 (s, 2H), 7.35-7.98 (m, 8H , Ar), 13.03 (s, 1H, NH); ^{13}C NMR (125 MHz, DMSO): 42.2, 108.3, 110.5, 115.3, 115.7, 124.6, 127.3, 135.7, 139.0, 142.0, 149.6, 159.0, 175.0 ppm. MS (m/z, %): 258 (M^+). Anal. Calcd. For $C_{13}H_{10}N_2O_2S$: C, 60.45; H, 3.90; N, 10.85. Found: C, 60.39; H, 3.81; N, 10.93.

3-Benzyl-2,3-dihydro-2-thioxoquinazolin-4(1H)-one, (4h)

White powder, m.p. 253-256 °C; IR: ($\nu_{max/cm}^{-1}$): 3200 (N-H), 3073(C-H), 1688 (C=O), 1177 (C=S); ^{1}H NMR (500 MHz, DMSO): δ= 5.67 (s, 2H), 7.23-7.96 (m, 8H , CH), 13.06 (s, 1H, NH); ^{13}C NMR (125 MHz, DMSO): 48.7, 115.4, 115.7, 124.6, 126.9, 127.1, 127.3, 128.2, 135.6, 136.5, 139.1, 159.3, 175.5 ppm. MS (m/z, %): 268 (M^+). Anal. Calcd. For $C_{15}H_{12}N_2OS$: C, 67.14; H, 4.51; N, 10.44. Found: C, 67.23; H, 4.47; N, 10.38.

RESULTS AND DISCUSSION

As mentioned above, synthesis of quinazolines have long been the subject of numerous studies and over the years of study several methods have been proposed for their synthesis. However, despite of this vast investigation there is scarce methods on synthesis of quinazolines in water using environmental friendly reagents. Organic reactions in watery solutions or without the use of harmful organic solvents have long been attracting much attention, because water is a very cheap, safe, and environmentally benign solvent. We describe here our findings regarding the synthesis of 2-thioxoquinazolin-4(1*H*)-one derivatives via condensation of isatoic anhydride, primary amines and phenylisothiocyanate in water by using potassium carbonate as catalyst at room temperature (Scheme 1).



Scheme 1. Synthesis of 2-thioxoquinazolin-4(1*H*)-ones via reaction of isatoic anhydride, primary amine and phenylisothiocyanate

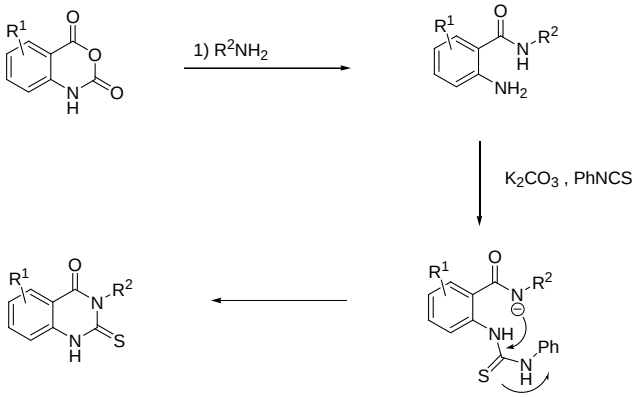
The synthesis was simply commenced by the reaction of isatoic anhydride and a primary amine in water to give the intermediate 2-aminobenzanilide, which subsequently subjected to reaction with phenylisothiocyanate to yield the

Table 1. Synthesis of various 2-thioxoquinazolin-4(1*H*)-ones from reaction of isatoic anhydride with different primary amines and isothiocyanates at room temperature in water.

Entry	R^1	R^2	MP (°C)	Yields (%)	Reaction Time (h)
4a	H	phenyl	307-309	75	3
4b	H	4-chlorobenzyl	317-319	71	3
4c	meta-Cl	phenyl	324-325	70	3.5
4d	H	$C_6H_5CH(CH_3)$	264-266	68	4
4e	H	$3,4\text{-}(MeO)_2C_6H_3CH_2$	302-305	72	5
4f	H	2-pyridylmethyl	294-297	69	4.5
4g	H	3-furylmethyl	278-280	66	4
4h	H	benzyl	253-256	74	4

expected intermediate 2-[(anilinocarbonothioyl)amino]-*N*-phenylbenzamide (Scheme 2). Removal of a proton from the later intermediate by K_2CO_3 promotes the intramolecular transimidation in this compound and accompanies with liberation of aniline to afford the 2-thioxoquinazolin-4(1*H*)-one products. All these processes were completed within nearly 3 hours under nitrogen at room temperature in water.

The IR spectrum of **4a**, for example, shows the characteristic vibration of N-H bond at 3247 cm^{-1}, the absorption band corresponding to vibration of aromatic C-H bonds at around 3067 cm^{-1}, and an strong band originating from C=O bond at 1664 cm^{-1}. The vibration of C=S bond appeared at 1197 cm^{-1}, which is relatively at higher wave number compared to the parent thiourea. ^{1}H NMR spectrum of this product shows a characteristic broad singlet for N-H at δ 13.03 in addition to the signals due to aromatic protons at δ 7.27–7.96 ppm. In ^{13}C NMR spectrum of compound **4a** the characteristic peak for C=S carbon appears downfield compared to that of C=O, in contrast to the trend in thioureas and ureas where the C=O carbon resonates at relatively lower field respect to the C=S carbon, hence for this product the resonance of C=S appeared at δ 176.0 and that of C=O appeared at δ 159.7 ppm.



Scheme 2. The reaction of isatoic anhydride, primary amine and phenyl isothiocyanate

Application of other ordinary bases such as NaOH and KOH to this reaction instead of K_2CO_3 in water led to lower yields, perhaps due to their advanced side reaction with phenylisothiocyanate. Variously substituted isothiocyanates were condensed with isatoic anhydride, a primary amine and phenylisothiocyanate in water by using potassium carbonate to give the desired 2-thioxoquinazolin-4(1*H*)-one derivatives in 66-75% yields completing within 3-5 hours (Table 1).

CONCLUSION

In summary, we have developed a facile and efficient method for synthesis of 2-thioxoquinazolin-4(1*H*)-one derivatives through reaction of isatoic anhydride, a primary amine and an isothiocyanate in water with the aid of K_2CO_3 as an available and cheap catalyst to afford excellent yields of the products.

This method also has the advantage to employ a homogeneous and environment friendly catalyst and therefore is ideal for industrial applications.

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