Quinoline-Based Polyazaheterocycles by a Hydrogen Peroxide-Mediated Isocyanide Insertion

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ABSTRACT
An efficient and green protocol for the synthesis of quinoline-based polyazaheterocycles with 2-(2-mercaptoquinolin-3-yl)-2,3-dihydroquinazolin-4(1H)-ones and aliphatic and aromatic isocyanides using hydrogen peroxide is described.

Introduction
Polyazaheterocycles are complex organic molecules that have received significant attention in the fields of dyes and pigments science, materials and polymer science, medicinal chemistry, and agrochemistry. Accordingly, the design and synthesis of diverse and complex heterocyclic systems from readily available starting materials are of high significance for synthetic and medicinal chemistry.

Quinoline- and quinazolinone-based polyazaheterocycles are fundamental motifs in numerous pharmaceuticals, natural products, and organic functional materials. For instance, they served as anticancer, anticonvulsant, anti-hypertensive, antiviral, and antibacterial properties. Furthermore, 1,2-fused quinazolinones are also used as potent inhibitors of TNF-α. Although several methodologies for the synthesis of 2,3-fused quinazolinone with diverse heterocycles have been reported, the synthetic strategies for the 1,2-fused quinazolinones are rare in the literature.

On the other hand, sulfur-containing organic compounds play an important role in functional materials, synthetic drugs, natural products, and even food. Among them, thiazine and its derivatives have exhibited a wide range of bioactivities such as 5-lipoxygenase inhibitor, anti-HIV, antidiabetic, antihistaminic, and antimycobacterial activities. According to the importance of quinolines, quinazolinones, and thiazines in medicinal chemistry, development of a new method for the combination of this three distinct pharmacophores into a single molecule can be interested in drug discovery programs.

In 2016, Berteina-Raboin group reported the synthesis of substituted 2-aminobenzothiazole derivatives using reaction of 2-aminothiophenol and isocyanides in the presence of H₂O₂ as oxidant and I₂ as a catalyst. Noteworthy performance of similar reaction in the presence of transition metals have also reported. In a continuation of our efforts on isocyanides chemistry and...
synthesis of biologically active heterocycles, herein, we wish to report a practical and efficient method for the preparation of quinolino-thiazino-quinazolinones (Scheme 1).

**Results and discussions**

To evaluate the feasibility, 2-(2-mercaptoquinolin-3-yl)-2,3-dihydroquinazolin-4(1H)-one 1a and cyclohexyl isocyanide 2a were initially chosen as the model substrates (Scheme 1, Table 1). At first, the reaction was performed in the presence of H$_2$O$_2$ (1.1 equiv.) and I$_2$ (5 mol%) in PEG$_{400}$ as described by Berteina-Raboin for 2-aminothiophenol. The desired product 3a was isolated in 61% yield (Table 1, entry 1). By increasing the amount of H$_2$O$_2$ to 2.2 equiv. the yield of 3a increased to 76% (Table 1, entry 2). Because of benefits of environmentally benign approaches we decided to remove I$_2$. It was found that in the absence of I$_2$, reaction needs 5 equiv. of H$_2$O$_2$ to be completed (Table 1, entry 3). Noteworthy, hydrogen peroxide constitutes a potentially green oxidant because it releases only water as by-product. Increasing the time to more than 2 h did not affect the yield of product any more. Screening of various solvents showed that THF is the best solvent for this two-component reaction in which 3a was isolated in 89% yield (Table 1, entry 4).

After having the optimal conditions, we investigated the generality of this reaction. To this end, various 2-(2-mercaptoquinolin-3-yl)-2,3-dihydroquinazolin-4(1H)-ones and isocyanides were applied to the reaction conditions to afford the desired products 3a–l (Figure 1). The reaction of 2-(2-mercaptoquinolin-3-yl)-2,3-dihydroquinazolin-4(1H)-ones bearing neutral and electron-donating substituents such as Me and OMe at different position of the quinoline ring with cyclohexyl and t-butyli isocyanides afforded the corresponding products 3a–c and 3f–i in 77–91% yields. Also, electron-withdrawing Cl group at the C-6 position of the quinoline ring provided desired products 3d and 3j in 85% and 82% yields, respectively. Furthermore, when 2-(2-mercaptobenzo[h]quinolin-3-yl)-2,3-dihydroquinazolin-4(1H)-one was used as substrate, the desired products 3k and 3l were isolated in 66% and 57% yields, respectively.

**Table 1.** Optimization of the reaction conditions.\(^a\)

| Entry | H$_2$O$_2$ (equiv.) | Solvent     | Yield 3a (%)\(^b\) |
|-------|---------------------|-------------|---------------------|
| 1\(^c\) | 1.1                 | PEG$_{400}$ | 61                  |
| 2\(^c\) | 2.2                 | PEG$_{400}$ | 76                  |
| 3      | 5                   | PEG$_{400}$ | 77                  |
| 4      | 5                   | THF         | 89                  |
| 5      | 5                   | EtOH        | 57                  |
| 6      | 5                   | PhCH$_3$    | 41                  |
| 7      | 5                   | DCM         | 30                  |
| 8      | 5                   | 1,4-dioxane | 82                  |
| 9      | 5                   | CH$_3$CN    | 62                  |

\(^a\)Reagents and conditions: 2-(2-mercaptoquinolin-3-yl)-2,3-dihydroquinazolin-4(1H)-one (1a) (1 mmol), cyclohexyl isocyanide (2a) (1.1 mmol), H$_2$O$_2$ in H$_2$O (30 wt%), solvent (2 mL), at 50 °C for 2 h.

\(^b\)Isolated yield.

\(^c\)I$_2$ (0.05 equiv.).
products 3e and 3k were obtained in good yields. Notably, phenyl isocyanide participated in the reaction to give the corresponding product 3l in 83% yield.

The structures of isolated products 3a–l were elucidated from their IR, 1H NMR, and 13C NMR spectra. The IR spectrum of 3a showed absorption band related to C=O bond of the amide group at 1677 cm⁻¹. The 1H NMR spectrum of 3a exhibited 10 protons related to five CH₂ of cyclohexyl ring at δ = 1.17–1.90 ppm and one more proton of cyclohexyl; CH, at δ = 3.68 ppm as multiplets. A doublet was observed at δ = 6.22 (J = 4.8 Hz) ppm for the methine moiety of the six-membered ring due to a vicinal coupling with the proton of the amide group. Nine aromatic H-atoms appeared in the region of δ = 7.01–8.35 ppm of the spectrum. Moreover,
one doublet at $\delta = 9.30$ (J = 4.4 Hz) ppm is seen for NH the amide group. The 13C NMR spectrum of 3a showed characteristic signals at $\delta = 24.3, 25.6, 33.3$, and 59.6 ppm for aliphatic carbons of cyclohexyl ring, a fairly shielded signal at $\delta = 66.0$ ppm due to the CH moiety of the six-membered ring, at $\delta = 153.7$ ppm for the C= N, as well as deshielded signal at $\delta = 162.6$ ppm arising from the amide carbonyl group. Fifteen other resonances (9 CH and 6 C) with appropriate chemical shifts were observed in the range of 116.8–147.7 ppm in agreement with the proposed structure.

Remarkably, this protocol employed for the synthesis of thiazino[6,5-b]quinolins 5 and gave desired products 5a and 5b in 91% and 87% yields, respectively (Scheme 2).
On the basis of the previous reports, a plausible mechanism for the present process can be suggested as depicted in Scheme 3. Initially, thiol 1 may be converted to disulfide A with hydrogen peroxide (H$_2$O$_2$). Next, the nucleophilic attack of isocyanide 2 on disulfide A gives intermediate B which underwent intramolecular cyclization through nucleophilic attack of the amine moiety of quinazolinone onto the nitrilium moiety to afford the corresponding product 3.

**Conclusion**

We have disclosed an efficient approach for the synthesis of thiazino[3,4-a]quinazolin-15(6H)-ones via two-component reaction between 2-(2-mercaptoquinolin-3-yl)-2,3-dihydroquinazolin-4(1H)-ones and isocyanides using H$_2$O$_2$ as oxidant. The main features of this reaction are high yields of the products, short reaction times, and easy work-up without any need for chromatographic purification process. Moreover, this approach provided a fast-track strategy to construct a complex core in one single operation from simple and easily accessible starting materials in an environmental friendly way.

**Experimental**

**General**

All chemicals were purchased from commercial sources. Melting points were taken by using a 9200-Branread Electrothermal. IR spectra were recorded on a Shimadzu Infra-Red Spectroscopy IR-435. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance 300 and 400 MHz spectrometer in DMSO-d$_6$ as a solvent.

**A typical procedure for the synthesis of thiazino[3,4-a]quinazolin-15(6H)-one 3a**

A mixture of 2-(2-mercaptoquinolin-3-yl)-2,3-dihydroquinazolin-4(1H)-one 1a (0.304 g, 1.0 mmol), cyclohexyl isocyanide 2a (0.109 g, 1.1 mmol), and an aqueous solution of H$_2$O$_2$ 30% (0.5 mL, 5.0 mmol) was stirred at 50°C for 2 h. After completion of the reaction as was indicated by TLC monitoring, the reaction mixture was cooled to room temperature. Next, the reaction mixture was extracted with CH$_2$Cl$_2$ (3 × 7 mL). The combined organic phase was dried over Na$_2$SO$_4$ and the solvent was removed under reduced pressure. Finally, the resulting precipitate was filtered, washed with EtOAc to afford the pure product 3a as a white solid.

**Spectroscopic data**

6-(Cyclohexylimino)-13b,14-dihydro-6H,15H-quinolino[3',2':5,6][1,3]thiazino[3,4-a]quinazolin-15-one (3a): White powder, mp: 292–297°C. FT-IR (KBr): $\nu_{\text{max}}$: 599, 1117, 1157, 1246, 1417, 1470, 1637, 1677, 2853, 2923, 3055, 3178 cm$^{-1}$. $^1$H NMR (400 MHz, DMSO-d$_6$): $\delta$ = 1.17–1.90 (m, 10H), 3.65–3.70 (m, 1H), 6.22 (d, $J$ = 4.8 Hz, 1H), 7.02 (t, $J$ = 7.6 Hz, 1H), 7.23 (d, $J$ = 7.2 Hz, 1H), 7.38 (t, $J$ = 7.2 Hz, 1H), 7.63 (t, $J$ = 7.6 Hz, 1H), 7.80–7.83 (m, 2H), 7.93 (d, $J$ = 8.4 Hz, 1H), 8.12 (d, $J$ = 7.6 Hz, 1H), 8.35 (s, 1H), 9.30 (d, $J$ = 4.4 Hz, 1H) ppm. $^{13}$C NMR (100 MHz, DMSO-d$_6$): $\delta$ = 24.3, 25.6, 33.3, 59.6, 66.0, 116.8, 119.1, 122.6, 126.4, 127.8, 128.1, 128.4, 128.5, 129.0, 131.6, 133.8, 133.9, 142.9, 144.3, 147.7, 153.7, 162.6 ppm.

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