UREA/THIOUREA AS AMMONIA SURROGATE: A CATALYST-FREE SYNTHESIS OF 2-SUBSTITUTED 2,3-DIHYDROQUINAZOLIN-4(1H)-ONES/QUINAZOLINE-4(3H)-ONES

P. Paradesi Naidu,1,2 Akula Raghunadh,1 K. Raghavendra Rao,1 Ramamohan Mekala,1 J. Moses Babu,3 B. R. Rao,1 V. Siddaiah,2 and Manojit Pal4

1Process Research and Development, Dr. Reddy’s Laboratories, Andhra Pradesh, India
2Organic Research Labs, Department of Organic Chemistry, Andhra University, Visakhapatnam, India
3Analytical Research, Custom Pharmaceutical Services, Dr. Reddy’s Laboratories, Hyderabad, India
4Dr. Reddy’s Institute of Life Sciences, University of Hyderabad Campus, Hyderabad, India

GRAPHICAL ABSTRACT

Abstract Urea/thiourea have been identified as an effective ammonia surrogate in the construction of quinazolin-4(3H)-one ring. This strategy afforded a simple and catalyst-free synthesis of 2-substituted 2,3-dihydroquinazolin-4(1H)-ones and quinazolin-4(3H)-ones via the reaction of isatoic anhydride and aryl aldehydes in the presence of urea or thiourea in ethanol. The reaction proceeded well to afford the quinazolin-4(3H)-one or its dihydro derivative, depending on the nature of carbonyl compounds employed.

Keywords Aldehyde; isatoic anhydride; quinazolin-4(3H)-one; urea

Received October 5, 2013.
Address correspondence to Manojit Pal, Dr. Reddy’s Institute of Life Sciences, University of Hyderabad Campus, Hyderabad 500046, India. E-mail: manojitpal@rediffmail.com

Color versions of one or more of the figures in the article can be found online at www.tandfonline.com/lsyc.

1475
INTRODUCTION

The development of new and efficient synthetic methods for the construction of nitrogen-containing heterocyclic rings is an important area of synthetic and medicinal chemistry, as many bioactive agents or drugs belong to this class of heterocycle. Quinazoline-4(3\(H\))-ones, because of their wide spectrum of biological and pharmacological activities, are one of the more extensively studied heterocyclic compounds in medicinal/pharmaceutical chemistry.\(^1\) For example, some quinazolinone-based natural products (e.g., febrifugine and isofebrifugine) have been identified as potential antimalarial agents. The 2,3-dihydroquinazolin-4(1\(H\))-ones, on the other hand, have also showed a broad range of pharmacological properties.\(^2\)

Various synthetic methods have been reported for the synthesis of quinazolin-4(3\(H\))-ones.\(^{3–8}\) Thus quinazolines can be prepared from 2-aminobenzaldehyde, 2-aminophenyl ketones, or anthranilic acids. For example, quinazolin-4(3\(H\))-ones are prepared from an anthranilic acid or its derivative, for example, 2-aminobenzonitrile and an amide in the presence of an acid catalyst at 200 °C (the Niementowski synthesis). Recently, a Yb(OTf)\(_3\)-catalyzed, one-pot, synthesis of quinazolin-4(3\(H\))-ones from anthranilic acid, anilines, and orthoesters (or formic acid) has been reported under solvent-free conditions.\(^9\) A number of synthetic methods have been reported for the synthesis of 2,3-dihydroquinazolin-4(1\(H\))-ones that include the use of iridium,\(^{10}\) citric acid,\(^{11}\) [bmim]HSO\(_4\),\(^{12}\) iodine,\(^{13}\) ammonium chloride,\(^{14}\) gallium trifluoromethanesulfonate,\(^{15}\) ionic liquids,\(^{16}\) Brookvsted acids,\(^{17}\) phosphoric acid,\(^{18}\) copper chloride,\(^{19}\) tetra butyl ammonium bromide,\(^{20}\) and TiCl\(_4\)/Zn.\(^{21}\)

While many of these methods are useful in various degrees, some of them still suffer from limitations such as unsatisfactory or variable yields, lengthy reaction time, unsatisfactory substrate tolerance, and more importantly the use of expensive or complex catalysts and reagents. Thus, development of an operationally simple, straightforward, and catalyst-free method is highly desirable. While the use of urea/thiourea as a reactant is common in organic synthesis (e.g., Biginelli reaction\(^{22}\)), their uses as ammonia surrogate is not common in the literature. Because of our continuing interest in quinazolinone derivatives,\(^{23}\) we now report the use of urea/thiourea as an effective ammonia surrogate in the construction of quinazolin-4(3\(H\))-one ring, affording a simple and inexpensive synthesis of 2-substituted 2,3-dihydroquinazolin-4(1\(H\))-ones/quinazoline-4(3\(H\))-ones (3 or 4) from isatoic anhydride 1 and aldehyde 2 in the presence of urea or thiourea (Scheme 1). To the best of our knowledge, this strategy has not been explored for the synthesis of 3 previously.

![Scheme 1](image)

**Scheme 1.** Catalyst-free synthesis of 2-substituted 2,3-dihydroquinazolin-4(1\(H\))-ones/quinazoline-4(3\(H\))-ones (3 or 4).
RESULTS AND DISCUSSION

In our initial study, isatoic anhydride (1) was reacted with 2-bromobenzaldehyde (2a) and urea in the absence of any catalyst in dimethylformamide (DMF) at 80–85°C for 6 h under open air when the corresponding 2,3-dihydroquinazolin-4(1H)-one (3a) was obtained in 90% yield (Table 1, entry 1). Notably, formation of any quinazoline-4(3H)-one was not observed in the present case. We then examined the use of other solvents such as ethanol, methanol, and water (Table 1, entries 2, 3, and 4), among which ethanol was found to be most effective as 3a was isolated in 90% yield (Table 1, entry 2). While 3a was isolated in poor yield in MeOH, the reaction did not proceed in water. The use of acetic acid, toluene, o-xylene, and acetone was also examined but found to be less or ineffective in terms of product yield (Table 1, entries 5–8). While urea was used as a reactant in all these reactions, the use of thiourea was also found to be equally effective as the reaction afforded 3a in 88% yield when urea was replaced by thiourea (Table 1, entry 9). Nevertheless, being an inexpensive and safer solvent, EtOH was chosen as a preferred solvent for further study. It is worth mentioning that while the formation of the corresponding quinazoline-4(3H)-one was not observed in the present case, its formation was noted in case of other aldehydes.

We then examined the generality and scope of this methodology. Accordingly, a variety of aryl aldehydes (2) were reacted with isatoic anhydride (1) in EtOH under the conditions of entry 2 of Table 1, and the results are summarized in Table 2. The reaction afforded the corresponding 2,3-dihydroquinazolin-4(1H)-ones (3) in excellent yields when aldehydes 2a–d were employed (Table 2, entries 1–4). In the case

| Entry | Solvent   | Yield (%) |
|-------|-----------|-----------|
| 1     | DMF       | 90        |
| 2     | EtOH      | 90        |
| 3     | MeOH      | 55        |
| 4     | H₂O       | 0         |
| 5     | Acetic acid | 20      |
| 6     | Toluene   | 0         |
| 7     | O-Xylene  | 0         |
| 8     | Acetone   | 10        |
| 9     | EtOH      | 88        |

aReaction conditions: All the reactions were carried out using isatoic anhydride 1 (0.003 mol), 2-bromobenzaldehyde 2a (0.0033 mol), and urea (0.0033 mol) in EtOH (4 mL) at 80–85°C under open air.

bIsolated yield.

cThiourea (0.0033 mol) was used in place of urea.
Table 2. Synthesis of 2-substituted 2,3-dihydroquinazolin-4(1H)-ones/quinazoline-4(3H)-ones (3 or 4)a

| Entry | Aldehyde (2) | Product (3 or 4) | Yieldb (%) | Yieldb,c (%) |
|-------|--------------|-----------------|------------|--------------|
| 1     | ![](image1) 2a | ![](image2) 3a  | 90         | 85           |
| 2     | ![](image3) 2b | ![](image4) 3b  | 92         | 80           |
| 3     | ![](image5) 2c | ![](image6) 3c  | 90         | 86           |
| 4     | ![](image7) 2d | ![](image8) 3d  | 90         | 88           |
| 5     | ![](image9) 2e | ![](image10) 3e | 95         | 82           |
| 6     | ![](image11) 2f | ![](image12) 3f | 83         | 76           |

(Continued)
| Entry | Aldehyde (2) | Product (3 or 4) | Yield<sup>b</sup> (%) | Yield<sup>b,c</sup> (%) |
|-------|-------------|-----------------|-----------------------|------------------------|
| 7     | ![2g](image) | ![3g](image)    | 87                    | 75                     |
| 8     | ![2h](image) | ![3h](image)    | 88                    | 80                     |
| 9     | ![2i](image) | ![3i](image)    | 90                    | 85                     |
| 10    | ![2j](image) | ![3j](image)    | 90                    | 82                     |
| 11    | ![2k](image) | ![3k](image)    | 85                    | 88                     |

<sup>a</sup>Reaction conditions: All the reactions were carried out using isatoic anhydride 1 (0.003 mol), aldehyde 2 (0.0033 mol), and urea (0.0033 mol) in EtOH (4 mL) at 80–85°C under open air.

<sup>b</sup>Isolated yield.

<sup>c</sup>Thiourea (0.003 mol) was used in place of urea.
of aldehydes 2e–k, the reaction seemed to proceed one step further, affording the quinazoline-4(3H)-ones (4) in good yields (Table 1, entries 5–11). While the reasons for these observations are not clearly understood, the participation of areal oxygen\[^{[24]}\] in these cases perhaps caused the formation of 4. Notably, a similar observation has been reported by Gao et al. while performing the synthesis of 2,3-dihydroquinazolin-4(1H)-one derivatives under their reaction conditions.\[^{[25]}\] Nevertheless, in addition to aryl aldehydes, the 1H-indole-3-carbaldehyde (2h) also participated well in the present reaction, affording the product 3h in 88% yield (Table 2, entry 8). The reaction did not proceed when ketones were employed in place of aldehydes (2), indicating the limitation of the present synthesis. The reaction was also not successful when aliphatic aldehyde (e.g., acetaldehyde) was used. While urea was used in all these reactions, we also examined the use of thiourea, which, like urea, afforded comparable yields of products 3 or 4 (Table 2).

A plausible mechanism for the present catalyst-free transformation is depicted in Scheme 2. The reaction seemed to proceed via the generation of intermediate E-1, which tautomerizes to the enol E-2 stabilized by the intramolecular H-bonding in a six-membered cyclic form. The amino group of E-2 then reacts with the aldehyde 2 to give the imine E-3, which on intramolecular cyclization afforded the intermediate E-4. The cleavage of \(-\text{N}–\text{C}=\text{X}\)- bond aided by EtOH at elevated temperature afforded 3. As shown in Table 2, 2,3-dihydroquinazolin-4(1H)-ones 3 formed in some of the cases underwent oxidation in the presence of air to give quinazoline-4(3H)-ones 4. To gain further evidence, the isatoic anhydride 1 was reacted with urea under the conditions of entry 2 of Table 1 when quinazoline-2,4(1H,3H)-dione was isolated as the only product (Scheme 3).

![Scheme 2. Proposed reaction mechanism.](image)

![Scheme 3. Reaction of isatoic anhydride 1 with urea in the absence of aldehyde.](image)
CONCLUSIONS

In conclusion, urea/thiourea has been identified as an effective ammonia surrogate in the construction of quinazolin-4(3H)-one ring for the first time. The methodology afforded 2-substituted 2,3-dihydroquinazolin-4(1H)-ones and quinazolin-4(3H)-ones via the reaction of isatoic anhydride and aryl aldehydes in the presence of urea or thiourea in ethanol. The methodology is operationally simple and does not involve the use of any metal,[26,27] other toxic, expensive catalysts/reagents,[28] and inert atmosphere. The limitations of this methodology are also discussed. Overall, the methodology is amenable for the generation of library of small molecules based on 2,3-dihydroquinazolin-4(1H)-ones and quinazolin-4(3H)-ones of potential pharmacological interest.

EXPERIMENTAL

Typical Method for the Synthesis of 2-(2-Bromophenyl)-2,3-dihydroquinazolin-4(1H)-one[24] (3a)

A mixture of isatoic anhydride 1 (3.0 mmol), 2-bromobenzaldehyde 2a (3.3 mmol), and urea (3.3 mmol) in EtOH (4.0 mL) was stirred at reflux for 6 h under open air. The progress of the reaction was monitored by thin-layer chromatography (TLC). After completion of the reaction, the mixture was concentrated under reduced pressure. The crude product obtained was crystallised from methanol to give the analytically pure compound as a colorless solid; 1H NMR (400 MHz, DMSO-d6) δ 8.19 (s, 1H, NH), 7.69–7.65 (m, 3H), 7.45 (t, J = 8.0 Hz, 1H), 7.35 (t, J = 8.0 Hz, 1H), 7.28 (t, J = 6.8 Hz, 1H), 6.98 (s, 1H, NH), 6.77 (d, J = 7.6 Hz, 1H), 6.74 (t, J = 8.0 Hz, 1H), 6.09 (s, 1H, CH); 13C NMR (DMSO-d6, 100 MHz) 163.6, 147.7, 139.1, 133.4, 132.8, 130.7, 129.1, 128.1, 127.4, 122.2, 117.5, 114.7, 114.6, 66.4; HRMS (ESI): calcd. for C14H12N2OBr, (M+H)+ 303.0133; found 303.0140.

ACKNOWLEDGMENTS

Help from the analytical department for the analytical data is appreciated. We thank Dr. Vyass and Kavi Raj for their helpful discussions.

FUNDING

We thank Dr. Reddy’s Laboratories Ltd. for the financial support and encouragement.

SUPPLEMENTAL MATERIAL

Supplemental data for this article can be accessed on the publisher’s website.

REFERENCES

1. For a recent review, see Michael, J. P. Nat. Prod. Rep. 2005, 22, 627–646.
2. See, for example, Chinigo, G. M.; Paige, M.; Grindrod, S.; Hamel, E.; Dakshanamurthy, S.; Czhuszcz, M.; Minor, W.; Brown, M. L. J. Med. Chem. 2008, 51, 4620–4631.
3. Yoo, C. L.; Fettinger, J. C.; Kurth, M. J. J. Org. Chem. 2005, 70, 6941–6943.
4. Kamal, A.; Reddy, K. S.; Prasad, B. R.; Babu, A. H.; Ramana, A. V. Tetrahedron Lett. 2004, 45, 6517–6520.
5. Alexandre, F. R.; Berecibar, A.; Wrigglesworth, R.; Besson, T. Tetrahedron 2003, 59, 1413–1419.
6. Shimizu, M.; Oishi, A.; Taguchi, Y.; Gama, Y.; Shibuya, I. Chem. Pharm. Bull. 2002, 50, 426–428.
7. Shalaby, A. A.; Ei-Khamry, A. M. A.; Shiba, S. A.; Ahmed, A. A. A. E. Arch. Pharm. Pharm. Med. Chem. 2000, 333, 365–372.
8. Stevenson, T. M.; Kazmierczak, F.; Leonard, N. J. J. Org. Chem. 1986, 51, 616–620.
9. Wang, L.; Xia, J.; Qin, F.; Qian, C.; Sun, J. Synthesis 2003, 1241–1244.
10. Jianguang, Z.; Jie, F. J. Org. Chem. 2011, 76, 7730–7736.
11. Ghorbani-Choghamarani, A.; Taghipour, T. Lett. Org. Chem. 2011, 8, 470–475.
12. Darvatkar, N. B.; Bhilare, S. V.; Deorukhkar, A. R.; Raut, D. G.; Salunkhe, M. M. Green Chem. Lett. Rev. 2010, 3, 301–306.
13. Zeng, L.-Y.; Cai, C. J. Heterocycl. Chem. 2010, 47, 1035–1039.
14. Shaabani, A.; Maleki, A.; Mofakham, H. Synth. Commun. 2008, 38, 3751–3759.
15. Chen, J.; Wu, D.; He, F.; Liu, M.; Wu, H.; Ding, J.; Su, W. Tetrahedron Lett. 2008, 49, 3814–3818.
16. Chen, J. X.; Su, W. K.; Wu, H. Y.; Liu, M. C.; Jin, C. Green Chem. 2007, 9, 972–975.
17. Rueping, M.; Antonchick, A. P.; Sugiono, E.; Grenader, K. Angew. Chem. Int. Ed. 2009, 48, 908–910.
18. Cheng, X.; Vellalath, S. K.; Goddard, R.; List, B. J. Am. Chem. Soc. 2008, 130, 15786–15787.
19. Abdel-Jalil, R. J.; Voelter, W.; Saeed, M. Tetrahedron Lett. 2004, 45, 3475–3476.
20. Davoodnia, A.; Allameh, S.; Fakhari, A. R.; Tavadakoli-Hoseini, N. Chin. Chem. Lett. 2010, 21, 550–553.
21. Shi, D. Q.; Rong, L. C.; Wang, J. X.; Zhuang, Q. Y.; Wang, X. S.; Hu, H. W. Tetrahedron Lett. 2003, 44, 3199–3201.
22. See, for example, Hazarkhani, H.; Karimi, B. Synthesis 2004, 1239–1242.
23. Kumar, K. S.; Kumar, P. M.; Reddy, M. A.; Ferozuddin, M.; Sreenivasulu, M.; Jafar, A. A.; Krishna, G. R.; Reddy, C. M.; Rambabu, D.; Kumar, K. S.; Pal, S.; Pal, M. Chem. Commun. 2011, 47, 10263–10265.
24. Wang, X.-S.; Yang, K.; Zhang, M.-M.; Yao, C.-S. Synth. Commun. 2010, 40, 2633–2646.
25. Gao, L.; Ji, H.; Rong, L.; Tang, D.; Zha, Y.; Shi, Y.; Tua, S. J. Heterocycl. Chem. 2011, 48, 957–960.
26. Song, Z.; Wan, X.; Zhao, S. Indian J. Chem. Tech. 2012, 19, 118–123.
27. Huang, C.; Fu, Y.; Fu, H.; Jiang, Y.; Zhao, Y. Chem. Commun. 2008, 6333–6335.
28. Zhou, J.; Fang, J. J. Org. Chem. 2011, 76, 7730–7736.