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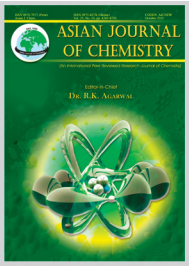

Efficient and Mild Synthesis of 2-Aryl-Substituted 2,3-Dihydroquinazolin-4(1*H*)-Ones Catalyzed by $NaHSO_4$

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Sodium hydrogen sulfate efficiently catalyzed in the condensation of anthranilamide with aromatic aldehydes under room temperature to afford 2-aryl-2, 3-dihydroquinazolin-4(1*H*)-ones in good yields and high purity. This methodology offers significant improvements with regard to the yield of products, inexpensive reagents and green aspects by avoiding toxic catalysts.

Key Words: $NaHSO_4$, 2,3-Dihydroquinazolin-4(1*H*)-ones, Room temperature, Environmentally friendly.

INTRODUCTION

Quinazolinone and its synthetic analogues are important heterocycles that attracted much attention due to their wide range of pharmaceutical and biological activities, such as antituberculos, antiinflammatory, anticancer, antibacterial and antifungal[1-5].

2,3-Dihydroquinazolin-4(1*H*)-ones, especially the 2-aryl substituted derivatives, are one of the important analogues, which have been found to exhibit a broad spectrum of biological activities such as anticancer, antifungal, diuretic, antifibrillatory and choleretic activities[6,7]. The same scaffold can also be found in some alkaloids isolated from traditional Chinese medicine[8]. Moreover, 2,3-dihydroquinazolin-4(1*H*)-ones can easily be oxidized to quinazolin-4(3*H*)-ones and the latter is another class of molecules with different pharmacological activities from those of its dihydro analogues[6,9].

The synthetic methodologies of 2,3-dihydroquinazolin-4(1*H*)-one derivatives have drawn much attention since 1960s due to their great importance. Amongst various methodologies reported for the preparation of quinazolins, there are three typical ways: (1) One-pot processes employing isatoic anhydride, ammonium and aldehyde as reactants[10]; (2) Reductive cyclization of *o*-nitrobenzamide using metallic reagents, which was always not environmental-friendly method[11]; (3) Third approach involves a condensation followed by a cyclodehydration between anthranilamide and aldehydes [6,10(a),12]. However, most of the reported protocols suffer from lengthy procedures and/or low yields and vigorous conditions[10(c),12]. Although hour used *p*-toluenesulfonic acid as a catalyst to get 2,3-dihydroquinazolin-4(1*H*)-ones under room temperature, it was mixed with quinazolin-4(3*H*)-ones[6]. Thus, a highly selective catalyst for the synthesis of quinazolins still remains a highly desired goal in organic synthesis.

In this paper, we report an efficient process of anthranilamide with aldehyde catalyzed by $NaHSO_4$ at room temperature in ethanol affording 2,3-dihydroquinazolin-4(1*H*)-ones in good yields and high purity.

EXPERIMENTAL

Solvents and reagents were commercially sourced and used without further purification or preparation. Melting points were taken on a Fischer-Johns micro hot-stage apparatus. ^{1}H NMR and ^{13}C NMR spectra were recorded on a VARIAN Mercury plus-300 instrument using tetramethylsilane (TMS) as an internal standard and DMSO-d_6 as the solvent at room temperature. Chemical shifts are given in d relative to tetramethylsilane, coupling constants (*J*) values are given in Hz. Mass spectra were measured with thermo finnigan LCQ-advantage.

General procedure for preparation of 3a-h: A mixture of anthranilimide (1 mmol), $NaHSO_4$ (0.5 mmol) and appropriate aldehyde (1 mmol) in EtOH (5 mL) was stirred at room temperature. The progress of the reaction was monitored by thin-layer chromatography (TLC). After completion, the ethanol was concentrated to dryness under vacuum. Water (15 mL) was added and the mixture was stirred for 2 min. The corresponding solid product was obtained through simple filtering, which was purified by chromatography over silica gel or recrystallized from ethanol.

Spectral data of the newly synthesized unreported compounds **3f-h** are given below:

2-(2-Chloro-6-fluorophenyl)l-2,3-dihydroquinazolin-4(1*H*)-one (3f): White solid, m.p. 176-177 ºC. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.22 (1H, s), 7.62 (1H, dd, *J* = 7.6, 1.3 Hz), 7.41-7.49 (1H, m), 7.36 (1H, d, *J* = 8.0 Hz), 7.19-7.29 (2H, m), 7.05 (1H, s), 6.60 - 6.68 (2H, m), 6.44 (1H, s). ^{13}C NMR (75 MHz, DMSO-d_6): δ 162.9, 162.1, 147.7, 133.6, 133.3, 131.3, 127.2, 126.1, 125.6, 116.8, 115.8, 113.9, 113.8, 62.2. LRESI-MS (m/z): 277 ($M+H^+$), HRESI-MS calc. for $C_{14}H_{10}N_2ONaClF$: 299.0363, found: 299.0351.

2-(5-Chloro-2-hydroxyphenyl)l-2,3-dihydroquinazolin-4(1*H*)-one (3g): White solid, m.p. 276-278 ºC. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.18 (1H, s), 7.98 (1H, s), 7.61 (1H, dd, *J* = 7.7, 1.4 Hz), 7.24-7.26 (1H, m), 7.16-7.22 (2H, m), 6.86 (1H, d, *J* = 5.7 Hz), 6.79 (1H, s), 6.74-6.77 (1H, d, *J* = 7.9 Hz), 6.64 (1H, td, *J* = 3.9, 1.2 Hz), 5.94 (1H, t, *J* = 1.7 Hz). ^{13}C NMR (75 MHz, DMSO-d_6): δ 163.9, 153.7, 147.9, 133.4, 129.2, 129.0, 127.4, 126.9, 122.3, 117.3, 117.2, 114.7, 114.6, 60.9. LRESI-MS (m/z): 275 ($M+H^+$), HRESI-MS calc. for $C_{14}H_{11}N_2O_2NaCl$: 297.0407, found: 297.0389.

2-(4-Methoxy-3-nitrophenyl)l-2,3-dihydroquinazolin-4(1*H*)-one (3h): White solid, m.p. 197-199 ºC. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.38 (1H, s), 7.98 (1H, d, *J* = 1.2 Hz), 7.76 (1H, dd, *J* = 8.8, 2.4 Hz), 7.61 (1H, dd, *J* = 7.7, 1.4 Hz), 7.40 (1H, d, *J* = 8.8 Hz), 7.26 (1H, td, *J* = 7.5, 1.7 Hz), 7.19 (1H, s), 6.76 (1H, d, *J* = 7.9 Hz), 6.68 (1H, m), 5.81 (1H, s), 3.91 (3H, s). ^{13}C NMR (75 MHz, DMSO-d_6): δ 163.6, 152.1, 147.6, 138.7, 134.1, 133.6, 132.9, 127.4, 123.5, 117.5, 115.0, 114.6, 114.4, 65.1, 56.9. LRESI-MS (m/z): 300 ($M+H^+$), HRESI-MS calc. for $C_{15}H_{13}N_3O_4Na$:322.0804, found: 322.0787.

RESULTS AND DISCUSSION

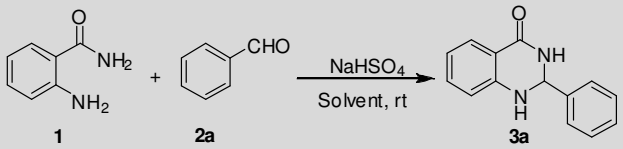
To optimize the solvents, the reaction of anthranilamide with benzaldehyde as a model experiment was examined in different solvents to get an insight into the solvent effect on the yields (Table-1). The results showed that ethanol was preferred over other solvents because of its low-cost, high yield and environmentally benign. Then the effect of amount of catalyst on the conversion rate of the reaction was studied by varying the amount of $NaHSO_4$ at room temperature (Table-1). It was found that 0.5 equivalent of $NaHSO_4$ was sufficient to carry out this reaction smoothly. An increase in the amount of $NaHSO_4$ to more than 0.5 equivalent showed no substantial improvement in the yield, whereas the yield was reduced by decreasing the amount of $NaHSO_4$ to 0.3 equivalent or none.

A wide variety of aldehydes were applied in the same procedure to prepare 2,3-dihydroquinazolin-4(1*H*)-ones[13]. As summarized in Table-2, benzaldehyde itself and benzaldehyde with electron-donating groups had a faster reaction speed and excellent yields, whereas those with electron-withdrawing group needed a longer reaction time, but the yields were also good (Table-2, Entries **a-e**). If there were two substituting groups, electronic effect and steric effect should both be considered (Table-2, Entries **f-h**).

Conclusion

In summary, we have discovered a concise and efficient route for the synthesis of 2,3-dihydro-quinazolin-4(1*H*)-ones in the presence of $NaHSO_4$ at room temperature. This protocol not only requires a simple procedure and provides 2-aryl-2,3-dihydro-quinazolin-4(1*H*)-ones in good yield with excellent purity, but also avoids the use of hazardous acids and harsh reaction condition. The advantages of this method are inexpensive catalyst, mild reaction condition and simple experimental operation. It provides a more practicable and efficient method for setting up pharmaceutical library. Efforts are under way to extend this principle of reaction for the straightforward access to other heterocyclic systems.

TABLE-1
OPTIMIZATION OF THE REACTION CONDITIONS FOR THE FORMATION OF 3a[a]

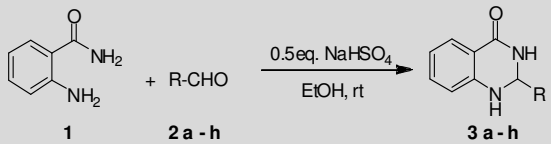


1 2a 3a

Entry	$NaHSO_4$ (eq)	Solvent	Yield[b] (%)
1	0.5	CH_3OH	92
2	0.5	DMF	89
3	0.5	DMSO	90
4	0.5	THF	61
5	0.5	C_2H_5OH	95
6	1.0	C_2H_5OH	94
7	0.3	C_2H_5OH	62
8	None	C_2H_5OH	Trace

[a]Reaction conditions: anthranilamide (1 mmol), benzaldehyde (1 mmol), $NaHSO_4$(eq) and ethanol (5 mL) at room temperature; [b]Isolated yields

TABLE-2
SYNTHESIS OF 2,3-DIHYDROQUINAZOLIN-4(1*H*)-ONES



1 2 a - h 3 a - h

Entry	R	Time	Yield [a] (%)	m.p. (ºC)
a	Ph	40 min	95	188-190[10 (a)]
b	2-HOC_6H_4	40 min	96	212-214[13]
c	4-$CH_3OC_6H_4$	30 min	97	187-189[6]
d	4-$CH_3C_6H_4$	30 min	95	201-202[13]
e	4-$NO_2C_6H_4$	4.5 h	96	195-197[10 (b)]
f	2-Cl-6-FC_6H_4	2.0 h	93	176-177
g	5-Cl-2-HOC_6H_4	1.5 h	91	276-278
h	4-CH_3O-3-$NO_2C_6H_4$	5.5 h	96	197-199

[a]Isolated yields

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REFERENCES

1. J.J. Caldwell, E.J. Welsh, C. Matijssen, V.E. Anderson, L. Antoni, K. Boxall and F. Urban, *J. Med. Chem.*, **54**, 580 (2011).
2. S.S. Parmar and R. Kumar, *J. Med. Chem.*, **11**, 635 (1968).
3. K.I. Ozaki, Y. Yamada, T. Oine, T. Ishizuka and Y. Iwasawa, *J. Med. Chem.*, **28**, 568 (1985).
4. A. Kamal, E.V. Bharathi, M.J. Ramaiah, D. Dastagiri, J.S. Reddy, A. Viswanath and F. Sultana, *Bioorg. Med. Chem.*, **18**, 526 (2010).

5. M.S. Mohamed, M.M. Kamel, E.M.M. Kassem, N. Abotaleb, S.I.A. El-Moez and M.F. Ahmed, *Eur. J. Med. Chem.*, **45**, 3311 (2010).
6. M.J. Hour, L.J. Huang, S.C. Kuo, Y. Xia, K. Bastow, Y. Nakanishi, E. Hamel and K.H. Lee, *J. Med. Chem.*, **43**, 4479 (2000).
7. (a) H.A. Parish Jr., R.D. Gilliom, W.P. Purcell, R.K. Browne, R.F. Spirk and H.D. White, *J. Med. Chem.*, **25**, 98 (1982); (b) G. Bonola, P.D. Re, M.J. Magistretti, E. Massarani and I. Setnikar, *J. Med. Chem.*, **11**, 1136 (1968).
8. J. Bergman and S. Bergman, *J. Org. Chem.*, **50**, 1246 (1985).
9. (a) R.J. Alaimo and C.J. Hatton, *J. Med. Chem.*, **15**, 108 (1972); (b) R. Y. Yang and A. Kaplan, *Tetrahedron Lett.*, **41**, 7005 (2000); (c) R.J. Abdel-Jalil, W. Voelter and M. Saeed, *Tetrahedron Lett.*, **45**, 3475 (2004).
10. (a) M. Dabiri, P. Salehi, S. Otokesh, M. Baghbanzadeh, G. Kozehgary and A.A. Mohammadi, *Tetrahedron Lett.*, **46**, 6123 (2005); (b) M. Baghbanzdeh, P. Salehi, M. Dabiri and G. Kozehgary, *Synthesis*, 344 (2006); (c) J.X. Chen, D.Z. Wu, F. He, M.C. Liu, H.Y. Wu, J.C. Ding and W.K. Su, *Tetrahedron Lett.*, **49**, 3814 (2008).
11. (a) M. Akazome, T. Kondo and Y. Watanabe, *J. Org. Chem.*, **58**, 310 (1993); (b) W. Su and B. Yang, *Aust. J. Chem.*, **55**, 695 (2002); (c) D. Shi, L. Rong, J. Wang, Q. Zhuang, X. Wang and H. Hu, *Tetrahedron Lett.*, **44**, 3199 (2003).
12. (a) J.P. Mayer, G.S. Lewis, M.J. Curtis and J. Zhang, *Tetrahedron Lett*., **38**, 8445 (1997); (b) M.J. Namkung and T.L. Fletcher, *J. Med. Chem.*, **13**, 329 (1970).
13. T.A. Kilroe-Smith and H. Stephen, *Tetrahedron,* **1**, 38 (1957).