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A novel method for the synthesis of 4(3*H*)-quinazolinones

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Abstract—Condensation of anthranilamide with aryl, alkyl or heteroaryl aldehydes in refluxing ethanol and the presence of $CuCl_2$ afforded the corresponding 2-substituted quinazolinones in excellent yields.

Quinazolinone derivatives have drawn much attention due to their broad range of pharmacological activities,[1] for example, anticancer,[2] antiinflammatory,[3] anticonvulsant[4] and antidituric[5] activities. Therefore, considerable efforts have been made to explore new simple and direct approaches towards the construction of 4(3*H*)-quinazolinone skeletons, for example, via cyclization of *o*-acylaminobenzamides,[6] amidation of 2-aminobenzonitrile followed by oxidative ring closure[7] and Pd-catalyzed heterocyclization of nitroarenes.[8] However, most of the reported methods suffer from tedious procedures and often from low yields. Therefore, simpler and high yield approaches towards this valuable nucleus is much desirable.

Herein, we want to present a high yield condensation of aryl, alkyl and heteroaryl aldehydes with anthranilamide to 4(3*H*)-quinazolinones. In the present study, the intermediate Schiff bases **2a**–**g** were synthesized within 3 h via condensation of anthranilamide **1** with the corresponding aldehyde in ethanol in 82–91% yields. The latter were converted within 2 h to the corresponding 4(3*H*)-quinazolinones **3a**–**g** in the presence of 3 equiv of copper chloride in refluxing ethanol.

Alternatively, these quinazolinone derivatives can also be prepared via one-pot procedure. Thus, anthranilamide, aldehyde and copper chloride were allowed to react in refluxing ethanol for 2–3 h to yield the corresponding 4(3*H*)-quinazolinones **3a**–**g** in 79–88 overall yield (Table 1). Typically, anthranilamide (1 mmol) was stirred with furfural (1.2 mmol) and copper chloride (3 mmol) in ethanol (100 mL) at 70–75 °C for 3 h to yield after conventional work up the 2-furan-2-yl-3*H*-quinazolin-4-one **3g** in 86% yield (Scheme 1).

Although, 2-substituted-4-quinazolinone nucleus has been similarly synthesized via condensation of anthranilamides with aldehydes followed by oxidation reaction using $NaHSO_3$[9] or DDQ[10] in good yields. Our present method has the advantage of the low temperature needed to achieve complete conversion of the anthranilimide to the quinazolinone derivatives.[11] The use of high temperature may produce complex decomposition mixtures.[10a]

In conclusion, an easy and simple method for 2-substituted-4(3*H*)-quinazolinones is reported. Efforts are currently under way to elucidate the mechanism of the conversion, especially the involvement of the copper

Table 1. Reaction conditions and yields of the quinazolinone **3a**–**e**

Entry	Solvent	Time (h)	Yield (%)
a	Ethanol	3	82
a	Methanol	3	71
a	2-Propanol	3	77
b	Ethanol	2	88
c	Ethanol	2.5	84
d	Ethanol	3	79
e	Ethanol	2	85
f	Ethanol	3	81
g	Ethanol	3	86

Keywords: Quinazolinone; Synthesis; Schiff base; Anthranilimide.
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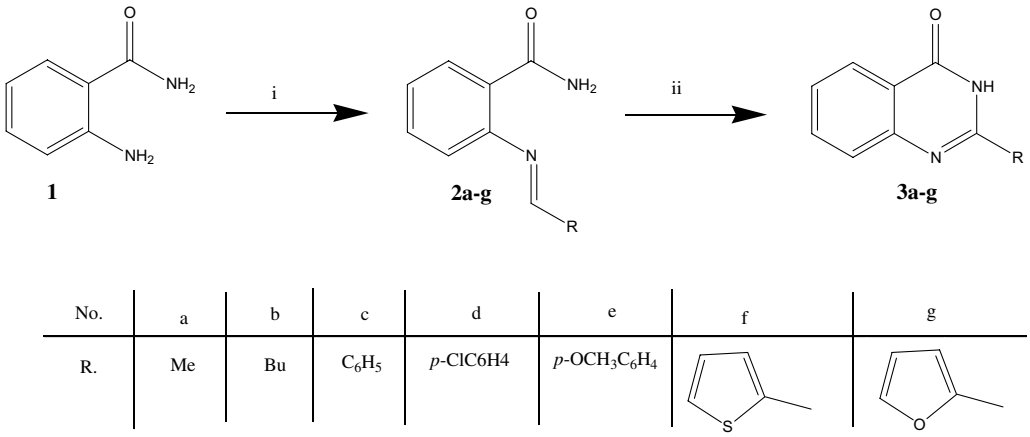

No.	a	b	c	d	e	f	g
R.	Me	Bu	C_6H_5	*p*-ClC6H4	*p*-$OCH_3C_6H_4$		

Scheme 1. Reagents and conditions: (i) RCHO, EtOH, 70 °C, 3 h; (ii) $CuCl_2$, EtOH, 70 °C, 3 h.

salt, and extend this principle of reaction for the straightforward access to other heterocyclic systems.

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References and notes

1. (a) Wolfe, J. F.; Rathman, T. L.; Sleevi, M. C.; Campbell, J. A.; Greenwood, T. D. *J. Med. Chem.* **1990**, *33*, 161–166; (b) Padia, J. K.; Field, M.; Hinton, J.; Meecham, K.; Pablo, J.; Pinnock, R.; Roth, B. D.; Singh, L.; Suman-Chauhan, N.; Trivedi, B. K.; Webdale, L. *J. Med. Chem.* **1998**, *41*, 1042–1049; (c) Khilil, M. A.; Soliman, R.; Farghaly, A. M.; Bekhit, A. A. *Arch. Pharm.* **1994**, *327*, 27–30.
2. Xia, Y.; Yang, Z. Y.; Hour, M. J.; Kuo, S. C.; Xia, P.; Bastow, K. F.; Nakanishi, Y.; Nampoothiri, P.; Hackl, T.; Hamel, E.; Lee, K. H. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1193–1196.
3. Kenichi, O.; Yoshihisa, Y.; Toyonari, O.; Toru, I.; Yoshio, I. *J. Med. Chem.* **1985**, *28*, 568–576.
4. Buchanan, J. G.; Sable, H. Z. In *Selective Organic Transformations*; Thyagarajan, B. S., Ed.; Wiley-Interscience: New York, 1972; Vol. 2, pp 1–95.
5. Lyle, F. R. U.S. Patent 5,973,257, 1985; *Chem. Abstr.* **1985**, *65*, 2870.
6. Armarego, W. L. F. *Adv. Heterocycl. Chem.* **1979**, *24*, 1–62.
7. Segarra, V.; Crespo, M. I.; Pujol, F.; Belata, J.; Domenech, T.; Miralpeix, M.; Palacios, J. M.; Castro, A.; Martinez, A. *Bioorg. Med. Chem. Lett.* **1998**, 505–510.
8. Akazome, M.; Yamamoto, J.; Kondo, T.; Watanabe, Y. *J. Organomet. Chem.* **1995**, *494*, 229–233.
9. Lopez, S. E.; Rosales, M. E.; Urdaneta, N.; Gody, M. V.; Charris, J. E. *J. Chem. Res. (S)* **2000**, *6*, 258–259.
10. (a) Deepthi, K. S.; Reddy, D. S.; Reddy, P. P.; Reddy, P. S. N. *Indian J. Chem., Sect. B* **2000**, *39*, 220–222; (b) Naleway, J. J.; Fox, C. M. J.; Robinhold, D.; Terpetsching, E.; Olsen, N. A.; Haugland, R. P. *Tetrahedron Lett.* **1994**, *46*, 8569–8572.
11. *General procedure for quinazolinone*: A mixture of anthranilimide (3 mmol), $CuCl_2$ (3 mmol) and the appropriate aldehyde (3.3 mmol) in ethanol (10 mL) was refluxed for 2–3 h. The reaction mixture was then allowed to cool to rt, the solvent was removed in vacuo, and the crude product was purified by column chromatography over silica gel to provide pure quinazolinone in high yields (Table 1). *Selected data*; compound **2g** (intermediate **2g** was purified by column chromatography for spectroscopic analysis): off white prisms, mp 162–164 °C (from ethanol), EI-MS; *m*/*z* 212, ^{1}H NMR (250 MHz, DMSO-d_6) δ: 5.82 (s, 1H, NH), 6.3 (br d, 1H, furyl), 6.43 (s, 1H, NH), 6.75 (m, 2H, furyl), 7.29, 7.67 (m, m, 2H, 2H, phenyl), 8.50 (s, 1H, N=CH); ^{13}C NMR (250 MHz, DMSO-d_6) δ: 105.7, 108.9, 113.5, 115.8, 125.9, 131.9, 141.3, 145.7, 153.1, 161.9. Compound **3g**: off white prisms, mp 218–220 °C, EI-MS; *m*/*z* 212, ^{1}H NMR (250 MHz, DMSO-d_6) δ: 6.98 (dd, 1.0, 2.3 Hz, 1H, furyl), 7.70–8.38 (m, 6H, phenyl+furyl), 12.76 (s, 1H, NH); ^{13}C NMR (250 MHz, DMSO-d_6) δ: 112.0, 114.0, 120.6, 125.4, 125.9, 126.7, 134.1, 143.5, 145.5, 146.1, 148.1, 161.0.