One-pot tandem approach for the synthesis of quinazolinones from *ortho*-aminobenzamides, benzyl halides and benzyl alcohols

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A one-pot tandem procedure is described for the synthesis of quinazolinones from benzyl halides or benzyl alcohols and *ortho*-aminobenzamides leading to the production of quinazolinones with high yields under mild conditions in DMSO without requiring an additional oxidant. According to the current method benzyl chlorides, benzyl bromides and benzyl alcohols bearing a range of substituents are suitable substrates.

Keywords: quinazolinones, *ortho*-aminobenzamides, benzyl halides, benzyl alcohol, one-pot tandem synthesis, nitrogenated heterocycles

Quinazolinones have emerged as an important class of nitrogenated heterocycles because of their pharmacological and therapeutic properties ranging from anticancer, diuretic, anti-inflammatory, anticonvulsant and antihypertensive activities.[1–4] There are a variety of procedures for producing quinazolinone scaffolds.[5] 2-Aryl/alkyl-4(3*H*)-quinazolinones are most commonly prepared using amidation of anthranilonitrile, anthranilic acid, or anthranilamide prior to cyclisation of the intermediate.[6–8] Methods involving condensation of imidates with anthranilic acid have also been reported.[9,10] Other approaches include using hetero Diels–Alder reaction of 1-aryl-4-dimethylamino-2-phenyl-1,3-diaza-1,3-butadienes and phenyl isocyanate,[11] or reaction of nitriles with lithiated anthranilamides.[12] Thermolysis of 3-arylideneamino-1,2,3-benzotriazin-4-ones,[13] and direct condensation of aldehydes and anthranilamide derivatives in the presence of $CuCl_2$ have also been reported.[14] One of the most frequently encountered heterocycles in medicinal chemistry is 4(3*H*)-quinazolinone. A literature survey revealed that there are many new routes affording corresponding quinazolinones. For example, Pd(II)-catalysed intramolecular C(sp^2)–H carboxamidation of *N*-arylamidines,[15] CuI/4-hydroxy-l-proline catalysed coupling of *N*-substituted *o*-bromobenzamides with formamide,[16] Pd-catalysed benzylic C–H amidation with benzyl alcohols,[17] palladium-catalysed N-monoarylation of amidines,[18] I_2/KI catalysed oxidative cyclocondensation of *o*-aminobenzamide with various aldehydes,[19] tetra-butylammonium bromide catalysed cyclocondensation of 2-aminobenzamide with aldehydes,[20] cellulosesulfonic acid catalysed condensation of 2-aminobenzamide with aldehydes or ketones,[21] chiral phosphoric acid catalysed transformation of 2-aminobenzamides with imines[22] and Zn[(L)-proline]2 catalysed cyclocondensation of 2-aminobenzamides with aryl aldehydes[23] are examples of these methods. In addition, an interesting multi-component reaction based on the use of isatoic anhydride as one of the starting materials for the synthesis of 2-arylquinazolin-4(3H)-ones has been reported.[24] By another approach, a tandem reaction between isatoic anhydride, a primary aniline or ammonium acetate, and triethylorthoacetate in the presence of imidazolium trifluoroacetate [Hmim]TFA has been reported.[25]

Most of the commonly used multi-step procedures suffer from shortcomings such as requiring long times for the reaction to be completed, low yields, harsh reaction conditions, difficult workups, and requiring expensive and toxic catalysts, media and reactants.

We now report a novel and efficient one pot method for the synthesis of 4(3*H*)-quinazolinones. According to this method, a mixture of *ortho*-aminobenzamides **1** and benzyl halides or benzyl alcohols **2** is used to afford 4(3*H*)-quinazolinones **3** in good yields of 78–86% (Scheme 1).

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Results and discussion

The reactions were performed at 90 °C by mixing the two components and were completed within 3 hours (Table 1). The structures of the products were established by ^{1}H NMR, ^{13}C NMR spectroscopy and by comparison of their spectral data and melting point values with those of the authentic samples reported in the literature.[26–28]

The procedure develops the known reaction, while not limiting one of the substrates to be an aldehyde. According to the mechanism of the reaction (Scheme 2), benzylic substrate **1** in DMSO is converted into the corresponding aldehyde **4** in the presence of K_2CO_3 at 90 °C under mild Kornblum oxidation conditions.[29–30] Subsequently the *in situ* prepared aldehyde is condensed with the *ortho*-aminobenzamides at 90 °C to yield the corresponding 4(3*H*)-quinazolinones **3** in 78–86% yields.

Conclusion

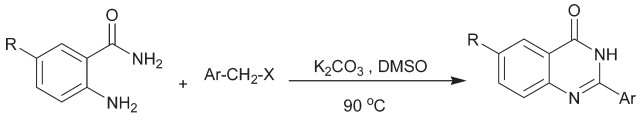
In summary, it can be concluded that an expedient and facile approach for the synthesis of 4(3*H*)-quinazolinones based on the feasibility of the use of the benzylic substrates has been developed. Benzyl chlorides, benzyl bromides and benzyl alcohols were found to be suitable substrates in this reaction, affording a range of 4(3*H*)-quinazolinones with good yields without having to use any additional oxidants.

Experimental

Chemicals and solvents were obtained from Merck (Germany) and Fluka (Switzerland) and were used without further purification. Melting points were measured on a Barnstead electrothermal melting point apparatus and were not corrected. ^{1}H NMR and ^{13}C NMR spectra were determined in DMSO-d_6 on a Bruker 500MHz NMR machine and chemical shifts were expressed in ppm downfield from tetramethylsilane.

Synthesis of 2-phenylquinazolin-4(3H)-one (entry a, Table 1); general procedure

A mixture of benzyl chloride (0.126 g, 1 mmol) and K_2CO_3 (1.5 mmol) in DMSO (1 mL) was stirred for 4 h at 90 °C. *ortho*-Aminobenzamide

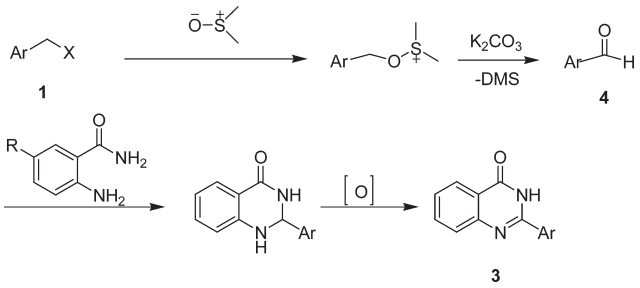


1 **2** **3**

Scheme 1

Table 1 Synthesis of 4(3*H*)-quinazolinones derivatives **3a–l**

3	Ar	X	R	Yield/%	M.p./°C	Lit. m.p./°C
a	C_6H_5	Br	H	82	236–238	235–237[27]
b	C_6H_5	Cl	H	80	236–238	235–237[27]
c	4-MeC_6H_4	Br	H	84	238–2240	238–240[27]
d	4-MeC_6H_4	Cl	H	80	238–2240	238–240[27]
e	4-MeC_6H_4	OH	H	86	238–2240	238–240[27]
f	C_6H_5	Br	Cl	81	288–290	287–289[27]
g	C_6H_5	OH	Cl	85	288–290	287–289[27]
h	C_6H_5	Br	Br	86	284–286	284–286[27]
i	4-$MeOC_6H_4$	Br	H	78	246–248	245–246[26]
j	3-FC_6H_5	Br	H	82	267–269	267[26]
k	C_6H_5	Br	Me	85	239–241	238–240[27]
l	C_6H_5	Br	NO_2	80	298–300	297–299[28]



Scheme 2 Mechanism of the reaction.

(0.136 g, 1 mmol) was added to the reaction mixture and stirring was continued at 90 °C for 2 h. The reaction mixture was cooled to room temperature and water (5 mL) was added. Stirring was continued for 1 h at ambient temperature. The resulting white precipitate was filtered, washed with water (5 mL), dried, and recrystallised from n-hexane/ethyl acetate (3:1) to give 2-phenylquinazolin-4(3*H*)-one as colourless crystals, m.p. 236–238 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 12.55 (s,br, 1H), 8.12–8.20 (m, 3H), 7.80–7.88 (m, 1H), 7.70–7.76 (m,1H), 7.55–7.62 (m, 4H) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz) δ 163, 153, 148.9, 134.9, 134.9, 133, 131.7, 128.8, 127.8,126.8, 126.0, 121.5 ppm.

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References

1 J.H. Chan, J.S. Hong, L.F. Kuyper, M.L. Jones, D.P. Baccanari, R.L. Tansik, C.M. Boytos, S.K. Rudolph and A.D. Brown, *J. Heterocycl. Chem*., 1997, **34**, 145.
2 D.A. Horton, G.T. Bourne and M.L. Smythe, *Chem. Rev*., 2003, **103**, 893.
3 A. Witt and J. Bergman, *Curr. Org. Chem*., 2003, **7**, 659.
4 Z.Z. Ma, Y. Hano and T. Nomura, *Heterocycles*, 2005, **65**, 2203.
5 D.J. Connoly, D. Cusack, T.P.O. Sullivan and P.J. Guiry, *Tetrahedron*, 2005, **61**, 10153.
6 T.L. Gilchrist, *J. Chem. Soc., Perkin Trans.*, 2001, **1**, 2491.
7 K. Hattori, Y. Kido, H. Yamamoto, J. Ishida, K. Kamijo, K.Murano, M. Ohkubo, T. Kinoshita, A. Iwashita, K. Mihara, S. Yamazaki, N. Matsuoka, Y. Teramura and H. Miyake, *J. Med. Chem*., 2004, **47**, 4151.
8 J.B. Jiang,, D.P. Hesson, B.A. Dusak, D.L. Dexter, G.L. Kang and E. Hamel, *J. Med. Chem*., 1990, **33**, 1721.
9 W. Ried and W. Stephan, *Chem. Ber*., 1962, **95**, 3042.
10 D.J. Connolly and P.J. Guiry, *Synlett*, 2001, 1707
11 P.D. Croce, R. Ferracioli and C. La Rosa, *Heterocycles*, 1997, **45**, 1309.
12 A. Couture, H. Cornet and P. Grandclaudon, *Synthesis*, 1991, 1009.
13 T.M. Paterson, R.K. Smalley and H. Suschitzky, *Synthesis*, 1975, 187.
14 R.J. Abdel-Jalil, W. Voelter and M. Saeed, *Tetrahedron Lett*., 2004, **45**, 3475.
15 B. Ma, Y. Wang, J. Peng and Q. Zhu, *J. Org. Chem.*, 2011, **76**, 6362.
16 L. Xu, Y. Jiang and D. Ma, *Org. Lett.*, 2012, **14**, 1150.
17 H. Hikawa, Y. Ino, H. Suzuki and Y. Yokoyama, *J. Org. Chem.*, 2012, **77**, 7046.
18 M.A. McGowan, C.Z. McAvoy and S.L. Buchwald, *Org. Lett.*, 2012, **14**, 3800.
19 M. Bakavoli, A. Shiri, Z. Ebrahimpour and M. Rahimizadeh, *Chinese Chem. Lett.*, 2008, **19**, 1403.
20 A. Davoodnia, S. Allameh, A.R. Fakhari and N. Tavakoli-Hoseini, *Chinese Chem. Lett.*, 2010, **21**, 550.
21 B.V. Subba Reddy, A. Venkateswarlu, C.H. Madan and A. Vinu, *Tetrahedron Lett.*, 2011, **52**, 1891.
22 D.J. Cheng, Y. Tian and S.K. Tian, *Adv. Synth Catal.*, 2012, **354**, 995.
23 N. Montazeri, K. Pourshamsian, M. Fouladi and M. Bayazi, *Orient. J. Chem*., 2012, **28**, 399.
24 M. Adib, E. Sheikhi and H. Bijanzadeh, *Synlett*, 2012, **23**, 85.
25 M. Dabiri, M. Baghbanzadeh, and A.S. Delbari, *J. Comb. Chem.* 2008, **10**, 700.
26 J. Chen, D. Wua, F. He, M. Liu, H. Wua, J. Ding and W. Su, *Tetrahedron Lett.*, 2008, **49**, 3814.
27 X. Zhang, D. Ye, H. Sun, D. Guo, J. Wang, H. Huang, X. Zhang, H. Jianga and H. Liu, *Green Chem*., 2009, **11**, 1881.
28 X.W. Liu, H. Fu, Y.Y. Jiang and Y.F. Zhao, *Angew. Chem. Int. Ed.*, 2009, **48**, 348.
29 N. Kornblum, W.J. Jones and G.J. Anderson, *J. Am. Chem. Soc*., 1959, **81**, 4113.
30 L.C. Li, Y. Xu, M. Lu, Z. Zhao, L. Liu, Z. Zhao, Y. Cui, P. Zheng, X. Ji and G. Gao, *Synlett*, 2002, **12**, 2041.