Iranian Journal of Organic Chemistry 1 (2009) 39-42

Molecular iodine oxidative cyclocondesation of *ortho*-aminobenzamide with aryl aldehydes: A new and efficient access to quinazolin-4(3H)-ones

Mehdi Bakavoli,* Mohammad Rahimizadeh, Ali Shiri, Zahra Ebrahimpour
Department of Chemistry, School of Sciences, Ferdowsi University of Mashhad, Mashhad 91775-1436, Iran

Abstract: A new and efficient access to quinazolin-4(3H)-ones by employing molecular iodine for the oxidative cyclocondensation of *ortho*-aminobenzamide with aryl aldehydes is presented. The reaction proceeded in a short period of time with excellent yields.

Keywords: Quinazolinone; Oxidative cyclization; Iodine; Cyclocondensation

Introduction

Quinazolin-4(3H)-ones are an important class of fused heterocycles with an array of biological activities such as inhibition of humane erythrocyte purine nucleoside phosphorylase [1] and poly(ADP-ribose) polymerase [2], treatment of diabetes and obesity [3], antagonist [4], anti-tumor [5], anti-inflamatory [6], insecticidal and anti-microbial [7] activity. They are also important building-blocks in total synthesis of natural products [8] and are the constituents of some isolated naturally occurring alkaloids [9]. The unique biological activities have made quinaqzolinone synthetic studies over the years very attractive. A review article covering the whole synthetic methods up to 2005 has appeared in the literature [10]. Multi step procedures, long reaction times, costly reagents, harsh reaction conditions, complex and tedious experimental procedures and low yields are the main drawbacks associated with some of these synthetic methods.

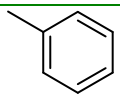
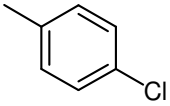
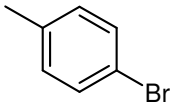
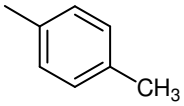
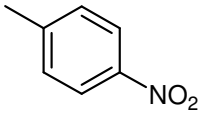
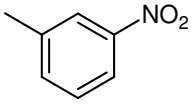
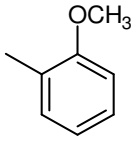
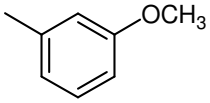
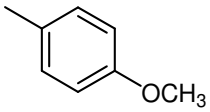
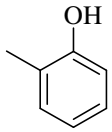
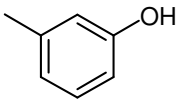
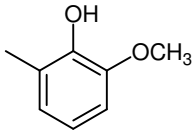
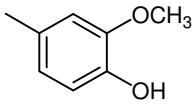
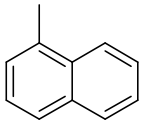
Recent advances in quinazoline syntheses include acid catalyzed cyclodehydration reactions using $KAl(SO_4)_2.12H_2O$ [11] and polyphosphoric acid [12], solid phase synthesis [13-14], Straudinger and intramolecular aza-Wittig reaction [15-16], Ullmann condensation using ultrasound irradiation [17], cyclocondensation of isothiocyanates with anthranilic acid [18] and H-Y zeolites induced heterocyclization of *ortho*-aminobenzamide under microwave irradiation [19]. A recent publication [22] reporting on the two-step synthesis of quinazolinones using hexamethyldisilazane-iodine induced cyclization of N-substituted benzamides with acylhalides and carboxylic acids , prompted us to pursue our ongoing effort [23-24] further towards the more efficient synthesis of quinazolinones and examine the prospect of the oxidative cyclodehydration of *ortho*-aminobenzamide with various aromatic aldehydes in the presence of molecular iodine as an inexpensive mild Lewis acid and oxidative reagent. In this study, various quinazolin-4(3H)-ones were prepared [29] (Table 1) by reacting *orhto*-aminobenzamide with different aldehydes in absolute ethanol. The reaction proceeded at room temperature within a short period of time after the addition of the molecular iodine to furnish the 2-aryl-quinazolin-4(3H)-ones **(3a-n)** in 76-99% yield (Scheme1, Table1). Only the reactions for compounds **3j**, **3k**, **3l**, **3m** and **3n**, had to be carried out under an atmosphere of argon or nitrogen.

1 **2** **3(a-n)**

Scheme 1

*Corresponding author. Tel: +(98) 511 8797022; fax: +(98) 511 8796416; E-mail: *mbakavoli@yahoo.com*

Table 1. Synthesis of quinazolinones **(3a-n)** via iodine cyclization of *ortho*-aminobenzamide with various aromatic aldehydes.

Product	-Ar	Time (min)	Yield (%)	mp(°C)	Lit. mp(°C)
3a		30	99	235-236	236[25]
3b		30	90	307-309	306[25]
3c		15	97	316	-
3d		5	99	240	241[25]
3e		10	83	363-264	362[26]
3f		10	80	355	354[26]
3g		35	92	207-209	208[25]
3h		5	88	207-208	210[25]
3i		10	95	247-248	247[25]
3j		30	97	296	297-298[27]
3k		30	98	255-257	-
3l		60	76	295-297	-
3m		50	85	270	-
3n		60	84	286-287	289[28]

The reaction of *ortho*-aminobenzamide with benzaldehyde as a model experiment was examined in different solvents to get an insight into the solvent effect on the yields and reaction times (Table2). As the result, absolute ethanol was preferred over other solvents because of its non-toxicity and low-cost, short reaction time and high yield. It is noteworthy that during oxidative dehydrative cyclisation of *ortho*-aminobenzamide with phenolic aldehydes, the hydroxyl groups remain intact to afford compounds **(3j-m)**.

Table 2. The solvent effects on time and yield of the reaction of *ortho*-aminobezamide with benzaldehyde

Entry	Solvent	Time(min)	Yield (%)
1	EtOH	10	99
2	MeOH	15	80
3	CH_2Cl_2	90	90
4	$CHCl_3$	120	94
5	CH_3CN	15	90
6	THF	120	60
7	DMSO	90	85

In conclusion, we have introduced a simple and efficient access to quinazolin-4(3H)-ones, by employing molecular iodine for the oxidative cyclocondesation of *ortho*-aminobenzamide with aryl aldehydes. We feel this protocol because of its simple experimental procedure and excellent yields will be useful for the synthesis of numerous fused heterocyclic compounds.

Experimental

General procedure for the synthesis of quinazolinones **3a-n**:
Ortho-amino-benzamide (1mmol, 0.136g) and various aromatic aldehydes (1.1mmol) were added in absolute ethanol (5mL). The solution was stirred for extra 5 min, and then iodine (1.1mmol, 0.25g) was added to it. The mixture was stirred according to the specified period of time (see Table1) and after the completion of the reaction which was monitored by TLC using chloroform : methanol (80:20) as eluent, water (10mL) was added to it and the resulting precipitate was filtered and washed with sodium thiosulphate solution (5%) and water ,respectively. Eventually, the solid was recrystallized from acetonitrile. For compounds **3j**, **3k**, **3l**, **3m** and **3n**, the reaction was carried out under the atmosphere of argon or nitrogene.

2-(4-bromophenyl) quinazolin-4(3H)-one (3c): ^{1}H NMR (100MHz, DMSO-d_6): δ 7.4-7.7 (d, 2H, *J* = 7.9 Hz Ar), 7.7- 8.1 (m, 4H, Ar), 8.3 (d, 2H, *J* = 7.3 Hz, Ar), 12.6 ppm (s, 1H, -NH); IR: ν 3375, 3040, 1673 cm^{-1}; EIMS: *m/z* 300 (100.0%), 302 (97.6%); Anal. calcd for $C_{14}H_9BrN_2O$: C, 55.84; H, 3.01; N, 9.30; Found C, 55.81; H, 2.98; N, 9.22.

2-(3-hydroxyphenyl) quinazolin-4(3H)-one (3k): ^{1}H NMR (100MHz, DMSO-d_6): δ 7.0 (d, 1H, *J* = 7.3 Hz Ar), 7.3- 7.8 (m, 4H, Ar), 8.1 (d, 1H, *J* = 7.4 Hz, Ar), 9.8 (s, 1H, -OH), 12.4 ppm (s, 1H, -NH). IR: ν 3390, 3200, 1670, 1110 cm^{-1}. EIMS: *m/z 238.* Anal. Calcd for $C_{14}H_{10}N_2O_2$: C, 70.58; H, 4.23; N, 11.76; Found C, 70.34; H, 4.09; N, 11.24.

2-(4-hydroxy-3-methoxyphenyl) quinazolin-4(3H)-one (3l): ^{1}H NMR (100MHz, DMSO-d_6): δ 3.8 (s, 3H, CH_3), 6.9 (d, 1H, *J* = 7.7 Hz, Ar), 7.4 (t, 2H, Ar), 7.6-7.9 (m, 3H, Ar), 8.2 (d, 1H, *J* = 7.3 Hz, Ar), 9.8 (s, 1H, -OH), 12.4(s, 1H, -NH); IR: ν 3390, 3200, 1670, 1110 cm^{-1}; EIMS: *m/z* 268. Anal. Calcd for $C_{15}H_{12}N_2O_3$: C, 67.16; H, 4.51; N, 10.44; Found C, 67.10; H, 4.42; N, 10.30.

2-(2-hydroxy-3-methoxyphenyl) quinazolin-4(3H)-one (3m): ^{1}H NMR (100MHz, DMSO-d_6): δ 3.8 (s, 3H, CH_3), 6.9-7.2 (m, 2H, Ar), 7.4-7.8 (m, 4H, Ar), 8.2 (d, 1H, *J* = 7.4 Hz, Ar), 12.5 (s, 1H, -NH), 14.1(s, 1H, -OH); IR: ν 3405, 3220, 1650, 1100 cm^{-1}; EIMS: *m/z* 268. Anal. Calcd for $C_{15}H_{12}N_2O_3$: C, 67.16; H, 4.51; N, 10.44; Found C, 67.02; H, 4.39; N, 10.13.

References

[1] Dempcy, R. O.; Skibo, E. B. *Biochemistry* **1991**, 30, 8480.
[2] Hattori, K.; Kido, Y.; Yamamoto, H.; Ishida, J.; Iwashita, A.; Mihara, K. *Bioorg. Med. Chem. Lett.* **2007**, 17, 5577.

[3] Rudolph, J.; Esler, W. P.; O'Connor, S.; Coish, P. D. G.; Wickens, P. L.; Brands, M.; Bierer, D. E.; Bloomquist, B. T.; Bondar, G.; Chen, L.; Chuang, C.; Claus, T. H.; Fathi, Z.; Fu, W.; Khire, U. R.; Kristie, J. A.; Liu, X.; Lowe, D. B.; McClure, A. C.; Michels, M.; Ortiz, A. A.; Ramsden, P. D.; Schoenleber, R. W.; Shelekhin, T. E.; Vakalopoulos, A. Tang, W.; Lei W.; Yi, L.; Gardell, S. J.; Livingston, J. N.; Sweet, L. J.; Bullock, W. H. *J. Med. Chem.* **2007**, 50, 5202.
[4] 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.
[5] Xia, Y.; Yang, Z.; Hour, M.; Kuo, S.; Xia, P.; Bastow, K. F.; Nakanishi, Y.; Nampoothiri, P.; Hackl, T.; Hamel, E.; Lee K**.** *Bioorg. Med. Chem. Lett.* **2001**, 11, 1193.
[6] Yadav, M. R.; Shirude, S. T.; Parmar, A.; Balaraman, R.; Giridhar, R. *Chem. Heterocycl. Compd.* **2006**, 1198
[7] Singh, T.; Sharma, S.; Srivastava, V. K.; Kumar, A. *Indian J. Chem., Sec. B, Org. Med. Chem.* **2006**, 45, 2558.
[8] Liu, J. *Curr. Org. Syn.* **2007**, 4, 223.
[9] Mhaske, S. B.; Argade N. P. *Tetrahedron* **2006**, 62, 9787.
[10] Connolly, D. J.; Cusack, D.; O'Sullivan, T. P.; Guiry P. J. *Tetrahedron* **2005**, 61, 10153.
[11] Dabiri, M.; Salehi, P.; Otokesh, S.; Baghbanzadeh, M.; Kozehgary, G.; Mohammadi, A. A. *Tetrahedron* **2006**, 46, 6123.
[12] Ivanov, I.; Nikolova, S.; Kochovska, E.; Statkova-Abeghe, S. *Heterocycles* **2006**, 68, 1443.
[13] Kundu, B.; Partani, P.; Duggineni, S.; Sawant, D. *J. Comb. Chem.* **2005**, 7, 909.
[14] Kamal, A.; Shankaraiah, N.; Devaiah, V.; Laxma Reddy, K.; *Tetrahedron Lett.* **2006**, 47, 9025.
[15] Eguchi, S.; *Arcivok* **2005**, 95.
[16] Blackburn, M.; Achab, A.; Elder, A.; Ghosh, S.; Guo, J.; Harriman, G.; Jones, M. *J. Org. Chem.* **2005**, 70, 10206.
[17] Pellón, R. F.; Docampo, M. L.; Kunakbaeva, Z.; Gómez, V.; Vélez-Castro, H. *Synth. Commun.* **2006**, 36, 481.
[18] El-Adasy, A. M.; *Phosphorus Sulfur Silicon Relat. Elem.* **2007**, 182, 2625.
[19] Bakavoli, M.; Sabzevari, O.; Rahimizadeh, M.; *Chin. Chem. Lett.* **2007**, 18, 533.
[20] Sharma, R. L.; Kumar, S.; Sachar, A.; Singh, J.; Kour, D. *Indian J. Heterocycl. Chem.,* **2006**, 16, 125.
[21] El-Khamry, A. A.; Shiba, S. A.; Shalaby, A. A.; Abd Alaha, A. A. *J. Heterocycl. Chem.* **2006**, 43, 1189.
[22] Kshirsagar, U. A.; Mhaske, S. B.; Argade, N. P. *Tetrahedron Lett.* **2007**, 48, 3243.
[23] Bakavoli, M.; Sabsevari, O.; Rahimizadeh, M. *Chin. Chem. Lett.* **2007**, 18, 1466.
[24] Rahimizadeh, M.; Tavallai, Z.; Bakavoli, M. *Indian J. Chem.* **2004**, 43B, 679.
[25] C. Mc Paterson, T.; Smalley, R. K.; Suschitzky, H. *Synthesis* **1975**, 187.
[26] Kilroe Smith, T. A.; Stephen, H. *Tetrahedron* **1957**, 1, 38.
[27] Naleway, J. J.; Fox, C. M. J.; Robinhold, D.; Terpetschnig, E.; Olson, N. A.; Haugland, R. P. *Tetrahedron Lett.* **1994,** 35, 8569.
[28] Xia, Y.; Yang, Z.; Hour, M.; Kuo, S.; Xia, P.; Bastow, K. F.; Nakanishi, Y.; Nampoothiri, P.; Hackl, T.; Hamel, E.; Lee K. *Bioorg. Med. Chem. Lett.* **2001**, 11, 1193.