$KAl(SO_4)_2•12H_2O$ (Alum) Catalyzed One-Pot Three-Component Synthesis of 2-Alkyl and 2-Aryl-4(3*H*)-quinazolinone under Microwave Irradiation and Solvent Free Conditions

Mohammadi, Ali A.*[,a] Sadat Hossini, S. S.[b]

[a] *Department of Chemistry, Sabzevar Branch, Islamic Azad University, Sabzevar, Iran*
[b] *University of Applied Science and Technology, Tehran P. O. Box 14155-1644, Tehran, Iran*

Twenty 2,3-disubstituted-4(3*H*)-quinazolinones were synthesed by one-pot three-component method with isatoic anhydride, orthoesters and amines as raw materials in the presence of $KAl(SO_4)_2•12H_2O$ (Alum) under microwave irradiation and solvent-free conditions. 6-Bromo-2-propyl-3-*p*-tolylquinazolin-4(3*H*)-one (**4m**), 6-bromo-2-methyl-3-phenethylquinazolin-4(3*H*)-one (**4n**) and 6-bromo-2-ethyl-3-phenethylquinazolin-4(3*H*)-one (**4o**) were characterized by IR, ^{1}H NMR, ^{13}C NMR and elemental analysis.

Keywords isatoic anhydride, orthoesters, ammonium acetate, 4(3*H*)-quinazolinone, multi component, microwave-assisted reactions

Introduction

4(3*H*)-Quinazolinones is a frequently encountered heterocycle in pharmacological literatures. Among the most important effects are hypnotic, anticonvulsant,[1] muscle relaxant,[2] analgesic,[3] antiinflammatory,[4] antibacterial[5] activites and as a potent non-nucleoside reverse transcriptase inhibitors, of human immunodeficiency virus (HIV-1).[6] These useful compounds are prepared by various methods.[7-9]

Multi-component reactions (MCRs) constitute an especially attractive synthetic strategy for rapid and efficient library generation due to the fact that the diversity can be achieved simply by varying the reacting components.

Experimental

Melting points were measured on the Electrothermal 9100 apparatus and are uncorrected. IR spectra were measured on a Shimadzu IR-470 Spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were determined on Bruker 300 DRX Avance instrument at 300 and 75 MHz, respectively. MS spectra were recorded on a Shimadzu QP 1100EX mass spectrometer operating at an ionization potential of 70 eV. Elemental analyses were performed using a Heracus CHN-O-Rapid analyzer.

General procedure

A mixture of isatoic anhydride (0.34 g, 2.5 mmol), orthoesters (4 mmol), amine (2.5 mmol), and $KAl(SO_4)_2•12H_2O$ (Alum) (0.1 g) in a tall beaker was placed in the microwave oven and beaker was covered with a stemless funnel and irradiated with power and time as indicated in Table 1. After completion of the reaction (monitored by TLC, ethyl acetate/*n*-hexane, 1/1), water (15 mL) was added to the reaction mixture, and the resulting solid was separated by filtration. The crude product was recrystallized from ethanol to give the pure product in good yield.

6-Bromo-2-propyl-3-p-tolylquinazolin-4(3*H*)-one (4m) 95%, m.p. 160—62 ℃; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.86 (t, J=7.3 Hz, 3H, CH_3), 1.66—1.78 (m, 2H, CH_2), 2.37 (t, J=7.8 Hz, 2H, CH_2), 2.47 (s, 3H, CH_3), 7.13 (d, J=8.1 Hz, 2H, Ar), 7.32 (d, J=8.1 Hz, 2H, Ar), 7.56 (d, J=8.7 Hz, 1H, Ar), 7.82 (dd, J=2.0, 8.7 Hz, 1H, Ar), 8.39 (d, J=2.0 Hz, 1H, Ar); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 0.03, 13.79, 20. 41, 21.33, 37.69, 119.83, 122.19, 127.87, 128.92, 129.45, 130.61, 134.38, 137.52, 139.46, 146.43, 157.68, 161.46; IR (KBr) v: 3063, 2972, 1679 (C=O) cm^{-1}; MS (70 eV) *m/z* (%): 357 (M^+, 25), 340 (35), 329 (100), 240 (30), 197 (60), 91 (50), 65 (35), 41 (25). Anal. calcd for $C_{18}H_{17}BrN_2O$: C 60.52, H 4.80, N 7.84; found C 60.40, H 4.71, N 7.76.

6-Bromo-2-methyl-3-phenethylquinazolin-4(3*H*)-one (4n) 94%, m.p. 140—42 ℃; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.44 (s, 3H, CH_3), 3.04 (t, J=7.5 Hz, 2H, CH_2), 4.28 (t, J=7.5 Hz, 2H, CH_2), 7.22—7.38 (m, 5H, Ar), 7.46 (d, J=8.7 Hz, 1H, Ar), 7.89 (dd, J=2.3, 8.7 Hz, 1H, Ar), 8.43 (d, J=2.3 Hz, 1H, Ar); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 23.19, 34.47, 46.61, 119.79, 121.86, 127.06, 128.61, 128.83, 128.88, 129.24, 137.45, 137.74, 146.11, 154.62, 160.85; IR (KBr) v: 3047, 2963, 1674 (C=O) cm^{-1}; MS (70 eV) *m/z* (%): 344 (M^+, 55), 138 (70), 222 (35), 104 (100), 91 (40), 75 (30), 65 (25). Anal.

* E-mail: Aliamohammadi@iaus.ac.ir
Received March 24, 2011; revised April 13, 2011; accepted May 10, 2011.

CHINESE JOURNAL OF CHEMISTRY

calcd for $C_{17}H_{15}BrN_2O$: C 59.49, H 4.41, N 8.16; found C 59.38, H 4.35, N 8.07.

6-Bromo-2-ethyl-3-phenethylquinazolin-4(3*H*)-one (4o) 93%, m.p. 116—118 ℃; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.32 (t, J=7.3 Hz, 2H, CH_3), 2.65 (q, J=7.3 Hz, 2H, CH_2), 2.98 (t, J=7.6 Hz, 2H, CH_2), 4.25 (t, J=7.6 Hz, 2H, CH_2), 7.23—7.40 (m, 5H, Ar), 7.49 (d, J=8.6 Hz, 1H, Ar), 7.87 (dd, J=2.2, 8.6 Hz, 1H, Ar), 8.43 (d, J=2.2 Hz, 1H, Ar); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 0.06, 11.34, 28.22, 34.71, 45.54, 119.69, 121.84, 126.98, 128.82, 128.86, 128.93, 129.16, 137.24, 137.78, 146.14, 157.97, 161.03; IR (KBr) v: 2971, 2925, 1677 (C=O) cm^{-1}; MS (70 eV) *m/z* (%): 358 (M^+, 35), 252 (85), 210 (35), 104 (100), 91 (25), 75 (25), 65 (35). Anal. calcd for $C_{18}H_{17}BrN_2O$: C 60.52, H 4.80, N 7.84; found C 60.42, H 4.73, N 7.73.

Results and discussion

We reported the preparation of quinazolinediones,[10] imidazoles,[11] 6-oxopyrano[2,3-*c*]isochromenes,[12] and 2-amino-4*H*-chromenes[13] via multi-component reactions. In addition, we have reported the ability of $KAl(SO_4)_2$•$12H_2O$ (Alum) as an effective catalyst in the synthesis of *cis*-isoquinolonic acid,[14] and di-hydropyrimidinones.[15] In view of this and also in continuation to our interest on multi-component reactions (MCR), we report herein, a simple, facile, rapid and efficient MCRs for the preparation of some new 2,3-disubstituted 4(3*H*)-quinazolinone derivatives with $KAl(SO_4)_2$•$12H_2O$ (Alum) as a nontoxic, inexpensive, very soluble in water, recyclable, and easy available reagent.

In the present work, we achieved a one-pot, three-component condensation of isatoic anhydride **1**, triethyl ortoacetate **2a**, and aniline **3a** on the surface of Alum under microwave irradiation as a new efficient method to produce 2-methyl-3-phenyl quinazolin-4(3*H*)-ones (**4a**) (Figure 1). Encouraged by this success, we extended this reaction to a range of other orthoesters **2b**—**2u** and amine **3b**—**3u** under similar conditions, furnishing the respective 2,3-disubstituted 4(3*H*)-quinazolinones (**4b**—**4u**) in good yields. The optimized results are summarized in Table 1. The structures of the products are supported by IR, ^{1}H NMR and ^{13}C NMR spectral data.

According to the results, the reaction can be mechanistically considered to proceed via the initial formation of the intermediates **5** from isatoic anhydride and amines, and then the former reaction followed by reac-

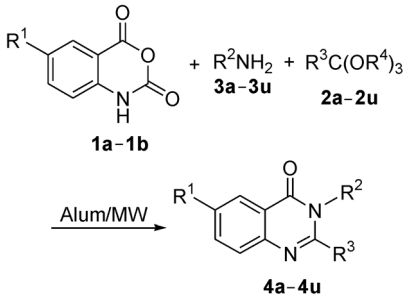

Figure 1 The synthetic route of the 2,3-disubstituted-4(3*H*)-quinazolinone (**4**).

Table 1 Synthesis of 2,3-disubstituted-4(3*H*)-quinazolinone **4**

Product **4**	R^1	R^2	R^3 (R^4)	Time/min	Yield[a]/%	m.p./℃	Lit. m.p./℃
4a	H	Ph	Me (Et)	5	96, 95, 93, 92[b]	144—146	145—146[16]
4b	H	*p*-ClC_6H_4	Me (Et)	6	96	158—159	157—158[17]
4c	H	*p*-MeC_6H_4	Ph (Me)	6	97	179—180	180—181[18]
4d	H	Ph	*n*-Pr (Me)	6	97	120—121	121—122[19]
4e	H	*p*-BrC_6H_4	Et (Et)	5	96	170—171	170—172[20]
4f	H	Et	Me (Et)	7	85	64—66	64—65[21]
4g	H	Me	Ph (Et)	5	82	129—131	131—132[22]
4h	H	Me	Me (Et)	5	92	195—197	194—196[18]
4i	H	*p*-EtC_6H_4	H (Et)	6	89	126—128	127—128[23]
4j	H	*p*-MeC_6H_4	H (Et)	6	90	143—144	144—145[24]
4k	H	$PhCH_2$	H (Et)	7	86	114—116	115—116[25]
4m	Br	*p*-MeC_6H_4	*n*-Pr (Et)	7	95	160—162	—
4n	Br	$PhCH_2CH_2$-	Me (Me)	6	94	140—142	—
4o	Br	$PhCH_2CH_2$-	Et (Me)	6	93	116—118	—
4p	H	H from (NH_4AcO)	H (Et)	6	92	214—215	216—218[26]
4q	H	H from (NH_4AcO)	Me (Et)	7	95	235—236	236—237[27]
4r	H	H from (NH_4AcO)	Et (Et)	7	96	235—236	235[28]
4s	H	H from (NH_4AcO)	*n*-Pr (Me)	7	94	197—198	206—207[28], 190[29]
4t	H	H from (NH_4AcO)	*n*-Bu (Me)	8	94	158—159	157[30]
4u	H	H from (NH_4AcO)	Ph (Et)	6	95	237—238	235—236[31]

[a] Isolated yields. [b] The same $KAl(SO_4)_2$•$12H_2O$ (Alum) was used for each of the four runs.

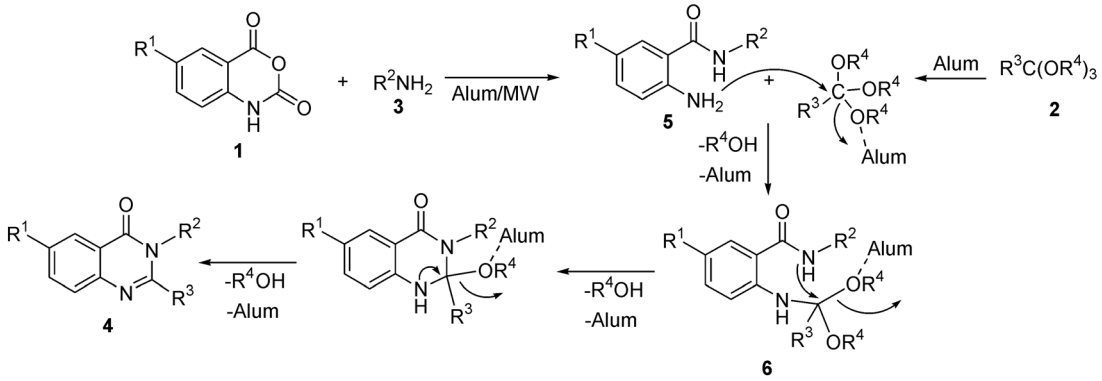

Figure 2 Plausible mechanism for the synthesis of 2,3-disubstituted-4(*3H*)-quinazolinone catalyzed by $KAl(SO_4)_2•12H_2O$ (Alum).

tion with orthoesters in the presence of alum gives the intermediate **6**. Once intermediate **6** is formed, a nucleophilic attack takes place by the nitrogen group, and then elimination of ROH and Alum occures to produce the final product (Figure 2).

Conclusions

In summary, we have described a successful strategy including an efficient and convenient green synthesis, for the preparation of some new 2,3-disubstituted-4-(3*H*)-quinazolinone in three-component cyclocondensation reaction of isatoic anhydride, orthoesters and amines. The method offers several advantages including high yield of products, using the inexpensive, nontoxic, and easily available $KAl(SO_4)_2•12H_2O$ catalyst, and an easy experimental workup procedure that makes it a useful process for the synthesis of 2,3-disubstituted-4(3*H*)-quinazolinones.

Acknowledgement

We gratefully acknowledge the financial support from the Research Council of Islamic Azad University, branched Sabzevar.

References

1 Johne, S. *Pharmazie* **1981**, *36*, 583.
2 Tani, J.; Yamada, Y.; Ochiai, T.; Ishida, R.; Inoue, I.; One, T. *Chem. Pharm. Bull*. **1979**, *27*, 2675.
3 Takesue, E. I.; Perrine, J. W.; Trapold, J. H. *Arch. Int. Pharmacodyn. Ther*. **1976**, *22*, 122.
4 Nawrocka, W.; Stasko, J. *J. Boll Chim. Farm.* **1998**, *137*, 35.
5 Sharma, S. D.; Kaur, V. *Synthesis* **1989**, 677.
6 Corbett, J. W.; Ko, S. S.; Rodgers, J. D.; Gearhart, L. A.; Magnus, N. A.; Bachheler, L. T.; Diamond, S.; Jeffrey, S.; Klabe, R. M.; Cordova, B. C.; Garber, S.; Logue, K.; Trainor, G. L.; Anderson, P. S.; Erickson-Vitanen, S. K.; Erickson-Vitanen, K. *J. Med. Chem*. **2000**, *43*, 2019.
7 Shateria, H. R.; Oveisi, A. R. *Chin. J. Chem.* **2009**, *27*, 2418.
8 Abou-Seri, S. M.; Abouzid, K.; Abou El Ella, D. A. *Eur. J. Med. Chem*. **2011**, *46*, 647.
9 Makino, S.; Suzuki, N.; Nakaishi, E.; Tsuji, T. *Synlett* **2000**, *11*, 1670.
10 Azizian, J.; Mohammadi, A. A.; Karimi, A. R. *Synth. Commun*. **2003**, *33*, 415.
11 Mohammadi, A. A.; Mivechi, M.; Kefayati, H. *Monatsh. Chem.* **2008**, *139*, 935.
12 Mohammadi, A. A.; Akbarzadeh, R.; Rohi, R. *Comb. Chem. High Throughput Screen*. **2009**, *12*, 536.
13 Makarem, S.; Mohammadi, A. A.; Fakhari, A. R. *Tetrahedron Lett.* **2008**, *49*, 7194.
14 Azizian, J.; Mohammadi, A. A.; Karimi, A. R.; Mohammadizadeh, M. R. *J. Org. Chem*. **2005**, *70*, 350.
15 Azizian, J.; Mohammadi, A. A.; Karimi, A. R.; Mohammadizadeh, M. R. *Appl. Catal. A*: *Gen.* **2006**, *300*, 85.
16 Kesarwani, A. P.; Srivastava, G. K.; Rastogi, S. K.; Kundu, B. *Tetrahedron Lett*. **2002**, *43*, 5579.
17 Grimmel, W.; Guenther, A.; Morgan, J. F. *J. Am. Chem. Soc*. **1946**, *68*, 542.
18 Levy, P. R.; Stephen, H. *J. Chem. Soc*. **1956**, 985.
19 Andrisano, R.; Chiesi, A. *Ateneo Parmense* **1961**, *32*, 671.
20 Jackman, G. B.; Petrow, V.; Stephenson, O. *J. Pharm. Pharmacol*. **1960**, 529.
21 Kato, T.; Takada, K. A.; Ueda, T. *Chem. Pharm. Bull*. **1976**, *24*, 431.
22 Al-Talib, M.; Jochims, J. C.; Hamed, A.; Wang, Q.; El-Hamid Ismail, A. *Synthesis* **1992**, 697.
23 Surendra, S.; Kishor, P. K.; Seth, P. K.; Arora, R. C. *J. Med. Chem*. **1969**, *12*, 138.
24 Nagahara, K.; Takagi, K.; Ueda, T. *Chem. Pharm. Bull*. **1976**, *24*, 1310.
25 Arndt, R. R.; Eggers, S. H.; Jordaan, A. *Tetrahedron* **1967**, *23*, 3521.
26 Higashino, T. *Yakugaku Zasshi* **1960**, *80*, 1404.
27 Boltze, K. H.; Dell, H. D.; Lehwaid, H.; lorenz, D.; Rueberg-Schweer, M. S. *Arzneimittel-forschung* **1963**, *13*, 688.
28 Patel, V. S.; Patel, S. R. *J. Indian Chem. Soc*. **1965**, *42*, 531.
29 Cohen, V. I. *J. Heterocycl. Chem*. **1978**, *15*, 1415.
30 Noland, W. E.; Jones, D. A. *Novel J. Org. Chem*. **1962**, *27*, 341.
31 Pater, R. *J. Heterocyclic. Chem*. **1971**, *8*, 699.

(E1103246 Sun, H.)

