Montmorillonite K-10 catalysed solvent-free synthesis of 2,3-disubstituted-4(3H)quinazolinones under microwave irradiation

M. Dabiri[a]*, P. Salehi[b], Ali A. Mohammadi[a], M. Baghbanzadeh[a] and Gh. Kozehgiry[a]

[a]*Department of Chemistry, Faculty of Science, Shahid Beheshti University, Tehran, 1983963113, Iran*

[b]*Department of Phytochemistry, Aromatic and Medicinal and Drugs Research Institute, Shahid Beheshti University, Tehran 1983963113, Iran*

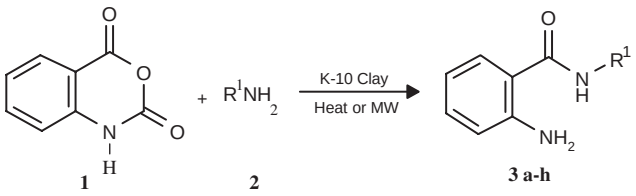
An efficient and rapid synthesis of 2,3-disubstituted-4(3*H*)quinazolinones by condensation of 2-aminobenzamide (substituted anthraniamides) with orthoesters in the presence of K-10 clay under solvent free conditions using microwave irradiation or classical heating is described.

Keywords: Montmorillonite K-10 clay, 2-aminobenzamide, orthoesters, solvent-free conditions, 2,3-disubstituted-4(3*H*)quinazolinones, icrowave irradiation

Clay minerals are known to catalyse a variety of organic reactions in which the clay catalyst acts as a solid Lewis or Brønsted acid.[1] Montmorillonite clay is inexpensive and offers several advantages over the conventional acids such as being non-corrosive, using mild reaction conditions, and giving high yields and selectivity. It is a non-polluting reagent with ease of set-up and work-up.[2] Microwave irradiation has been extensively used for the rapid synthesis of a variety of heterocyclic compounds.[3] Microwave irradiation in solvent-free conditions has also shown its utility in organic synthesis.[4] Due to the potential use of many derivatives of 2,3-disubstituted-4(3*H*)quinazolinones, as pharmaceutically active compounds,[5,6] synthesis of this class of compound has been extended. The most simple and straightforward procedure, reported by Niementowski in 1895 involves the condensation of a 2-aminobenzoic acid with amides.[7] Other methods reported recently involve the cyclocondensation of different substrates such as: 2-nitrobenzyl chloride with arylamines,[8] anthranilic acid with amino acids and aldehydes,[9] thioureas with isatoic anhydride,[10] and 2-fluoro substituted benzoyl chlorides with 2-amino-*N*-heterocycles.[11]

Very recently the synthesis of these useful compounds has been reported by multi-step reactions under microwave irradiation.[12] Here we report an easy and efficient synthesis of 2,3-disubstituted-4(3*H*) quinazolinones by the condensation of 2-aminobenzamides (substituted anthranilamides) and orthoesters on montmorillonite K-10 under either conventional heating or microwave irradiation in the absence of solvent in high yields.

In a typical case, isatoic anhydride **1** and primary amines **2** were mixed in an Erlenmeyer flask, and irradiated with microwaves (300 W power) for 1 min. Work-up of the reaction mixture showed that 2-aminobenzamides **3a–3h** are prepared in 80-90% yield after recrystallisation from ethanol (Scheme 1 and Table 1).



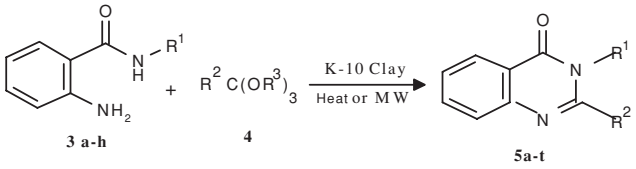
1 **2** **3 a-h**

Scheme 1

Furthermore, we have found that the 2-aminobenzamides **3a**–**3h** were converted into 2,3-disubstituted-4(3*H*) quinazolinones **5a**–**5t** on reaction with orthoesters **4** on montmorillonite K-10 in a very short period of irradiation with microwave or on classical heating under solvent-free conditions (Scheme 2, Table 2).

In all cases, the yields were optimised by interrupting the reactions, and monitoring the progress of the reaction by thin layer chromatography. The results are summarised in Table 2.

Different kinds of substituted aromatic amines were subjected to the reaction with isatoic anhydride, and the related 2-aminobenzamides (substituted anthranilamides) were isolated in good yields under microwave irradiation (irradiation conditions were 210 W, 1 min and 385 W, 1 min) or conventional heating in the absence of solvent (Table 1, entries 2–5 and 8). 2-Phenylethylamine, benzylamine, and ethylamine were also reacted satisfactorily under the same conditions (Table 1, entries



3 a-h **4** **5a-t**

Scheme 2

Table 1 The synthesis of 2-aminobenzamides **3a–3h**

Entry	Product	R^1	Lit.Yield/%	MW (Heat) yield/%[a,b]	Lit. m.p./°C	M.p./°C
1	**3a**	Et	87	92 (83)	102–103[13]	100–101
2	**3b**	Ph	79	82 (80)	125.5–126.5[13]	123–125
3	**3c**	*p*-BrC_6H_4	70	85 (72)	147.5–149[13]	146–148
4	**3d**	*p*-ClC_6H_4	72.3	89 (70)	140–141.5[13]	140–141
5	**3e**	*p*-MeC_6H_4	83.2	87 (85)	150–151.5[13]	149–150
6	**3f**	$PhCH_2$-	69	90 (83)	123–123.5[13]	123–125
7	**3g**	$PhCH_2$-CH_2	–	80 (72)	–	91–92
8	**3h**	*p*-EtC_6H_4	–	86 (79)	145–146[18]	144–145

[a]Yield of pure, isolated product based on isatoic anhydride.
[b]To control the reaction, the irradiation was carried out in two stages (irradiation conditions were [1] 210 W, 1 min and [2] 385 W, 1 min).

* Correspondence. Email: m-dabiri@cc.sbu.ac.ir

Table 2 Synthesis of 2,3-disubstituted quinazolinones **5a–t**

Entry	Product	R^1	R^2	R^3	Heat[a] (Lit. yield) %	MW yield[a,b] %	M.p./°C	Lit.m.p. /°C
1	**5a**	*p*-ClC_6H_4	Me	Et	82 (80[14])	90	158–159	157–158[14]
2	**5b**	*p*-MeC_6H_4	Me	Et	75 (40[17])	81	148–149	148–150[17]
3	**5c**	Ph	Me	Et	80 (38[17])	87	144–146	145–146[17]
4	**5d**	Ph	Ph	Me	74 (90[16])	88	157–159	158–159[16,22]
5	**5e**	*p*-MeC_6H_4	Ph	Me	72 (61[20])	84	179–180	180–181[19]
6	**5f**	*p*-ClC_6H_4	Ph	Me	80	88	190–192	190–191[14]
7	**5g**	*p*-MeC_6H_4	Et	Et	79	86	162–163	163–164[15]
8	**5h**	*p*-MeC_6H_4	*n*-Pr	Me	81	91	145–147	145–146[15]
9	**5i**	Ph	*n*-Pr	Me	78	92	120–121	121–122[15]
10	**5j**	*p*-EtC_6H_4	Me	Et	70 (66[14])	78	151–152	150–152[18]
11	**5k**	*p*-BrC_6H_4	Et	Et	84	91	170–171	170–172[18]
12	**5l**	*p*-BrC_6H_4	*n*-Pr	Et	78	80	138–140	139–141[18]
13	**5m**	$PhCH_2$–	Me	Et	82 (31[17],88[21])	92	230–231	230–232[17]
14	**5n**	Et	Et	Et	85 (35[17])	90	96–97	95–96[17]
15	**5o**	Et	Me	Et	80 (22[17])	80	64–66	64–65[17]
16	**5p**	$PhCH_2$–CH_2–	Me	Et	82	87	100–101	–
17	**5q**	$PhCH_2$–CH_2–	Et	Et	74	78	103–105	–
18	**5r**	$PhCH_2$–CH_2–	*n*-Pr	Me	81	83	105–106	–
19	**5s**	$PhCH_2$–CH_2–	*n*-Bu	Me	80	85	109–110	–
20	**5t**	$PhCH_2$–CH_2–	Ph	Me	75	82	175–176	–

[a]Yield of pure, isolated product based on 2-aminobenzamide.
[b]To control the reaction, the irradiation was carried out in two stages (irradiation conditions were [1] 210 W, 3 min and [2] 385 W, 3 min).

1, 6 and 7). These syntheses were found to be feasible by interaction of anthranilamides and orthoesters to form the 2, 3-disubstituted-4(3*H*)quinazolinones on montmorillonite K-10 under solvent-free conditions in high yields. Comparison with the percentage yield of those compounds reported previously,[14,16-7,20-1] showed that the yields obtained in this way, under microwave irradiation or conventional heating, are most satisfactory (Table 2). The catalyst is recyclable and can be used several times without any decrease in the product yield. In summary, we have described a facile and efficient procedure for the preparation of some novel 4(3*H*)quinazolinones using the inexpensive, non-toxic and readily available K-10 clay catalyst. The method offers several advantages including high yield of products, short reaction times, solvent-free conditions, cleaner reactions and an easy experimental work-up procedure.

Experimental

Products **3a**–**f** and **5a**–**o** are known compounds and their physical data, IR and ^{1}H NMR spectra were essentially identical with those of authentic samples. Products **5p**–**t** are new compounds and characterised by their spectroscopic data (IR, ^{1}H, and ^{13}C NMR, M.S., and elemental analysis). Melting points were obtained in open capillary tubes and also were measured on the Electrothermal 9100 apparatus and are uncorrected. Mass spectra were recorded on a Shimadzu QP 1100 BX Mass Spectrometer operating at an ionisation potential of 70 eV. CHN Elemental analyses were performed using a Heracus CHN–O–Rapid analyzer. IR spectra were recorded on KBr pellets on a Shimadzu IR-470 Spectrophotometer. ^{1}H and ^{13}C NMR spectra were determined on a Bruker 500 DRX AVNCE instrument at 500 and 125 MHz, respectively. Microwave irradiation was carried out in a conventional National oven, model 5250 at 2450 MHz.

General procedure under conventional heating

A stirred mixture of isatoic anhydride **1** (1.034 g, 0.008 mol) and the amine **2** (0.01 mol) was heated at 60 °C for 1 h. The crude product recrystallised from 96% ethanol gave 2-aminobenzamides **3a**–**3h** in good yield (Table 1). 2-Aminobenzamides **3a**–**3h** were heated at 80°C for 2 h with orthoesters **4** (2 ml) in the presence of catalytic amounts of montmorillonite K-10 (0.3 g) under solvent-free conditions to form 2,3-disubstituted-4(3*H*)quinazolinones **5a**–**5t**. The solid product was washed with hot EtOH. After cooling it to room temperature, the solvent was evaporated and the crude product recrystallised from ethanol. Yields are given in Table 2. In all cases, the yields were optimised by interrupting the reactions at each 30 min period and monitoring the progress of the reaction by TLC.

General procedure under microwave irradiation

Isatoic anhydride **1** (1.034 g, 0.008 mol), amine **2** (0.01 mol) were mixed thoroughly in an Erlenmeyer flask which was then placed in the microwave oven and the mixture was irradiated for two subsequent 1 min periods (irradiation conditions were [1] 210 W, 1 min, [2] 385 W, 1 min). The reaction mixture was allowed to cool to room temperature and the resultant residue was washed with hot EtOH. After cooling, the solvent was evaporated under reduced pressure and the crude solid product was recrystallised from EtOH to afford the pure products **3a**–**3h** (Table 1). The resulting 2-aminobenzamides, orthoesters **4** (2 mol) and K-10 clay (0.3 g) were mixed thoroughly in a tall beaker, covered with a stemless funnel and then placed in the microwave oven. The mixture was irradiated for two subsequent 3 min periods (irradiation conditions were [1] 210 W, 3 min, [2] 385 W, 3 min). The precipitates were filtered, washed with hot ethanol and cooled to room temperature. The crude product was recrystallised from 96% ethanol or absolute ethanol to give products **5a**–**5t** (Table 2). In all cases, the yields were optimized by interrupting the reactions at each 1 min period and monitoring the progress of the reaction by TLC.

Spectral data for products 3g and 5p-t

2-Aminobenzphenylethyl anilide **(3g) :** white crystals, m.p. 91–92 °C. IR (KBr), (ν_{max}/cm^{-1}): 3440, 3290, 1610 (C=O). ^{1}H NMR ($CDCl_3$) δ_H: 3.82 (t, *J*=7.81 Hz, 2H, CH_2), 4.92 (m, 2H, CH_2), 4.85 (broad, 2H, NH_2), 9.25 (broad, 1H, NH), 7.23–8.15 (m,9H). ^{13}C NMR ($CDCl_3$) δ_C: 34.74, 46.59, 120.62, 126.38, 126.51, 126.58, 126.73, 128.64, 134.o5, 137.65, 147.12, 154.01, 161.13. MS (*m/z*, %): 240 (M^+, 63.52),119 (60.46), 104 (70.43), 77 (51.26). Anal. Calcd for $C_{15}H_{16}N_2O$: C, 74.97; H, 6.71; N,11.66; Found: C,74.83; H, 6.59; N,11.62.

2-Methyl-3-phenylethyl-4(3H)quinazolinone **(5p) :** white powdery crystals, m.p. 100–101 °C. IR (KBr), (ν_{max}/cm^{-1}): 1680 (C=O). ^{1}H NMR ($CDCl_3$) δ_H: 2.9 (s, 3H, CH_3), 3.55 (t, *J*=7.64 Hz, 2H, CH_2), 4.78 (t, *J*=7.64 Hz, 2H, CH_2), 7.71-8.23 (m, 8H), 8.77 (dd, *J*=1.07 Hz, *J*=6.88 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ_C: 23.13, 34.65, 46.51, 120.56, 126.47, 126.70, 126.74, 126.98, 128.87, 134.28, 137.97, 147.29, 154.14, 162.02 (C=O). MS (*m/z*, %): 264 (M^+, 38.5), 105 (73.5), 119 (45.2), 93 (37.2), 77 (51.2). Anal. Calcd for $C_{17}H_{16}N_2O$: C, 77.27; H, 6.06; N, 10.56; Found: C, 77.41; H, 6.21; N, 10.56.

2-Ethyl-3-phenylethyl-4(3H)quinazolinone **(5q):** fibrous crystals, mp 103–104°C. IR (KBr), (ν_{max}/cm^{-1}): 1680 (C=O). ^{1}H NMR ($CDCl_3$) δ_H: 1.84 (t, *J*=7.39 Hz, 3H, CH_3), 3.21 (q, *J*=7.38 Hz, 2H, CH_2), 3.54 (t, *J*=7.76 Hz, 2H, CH_2), 4.79 (t, *J*=7.79 Hz, 2H, CH_2), 7.74–8.23 (8H, m), 8.79 (dd, *J*=0.57 Hz, *J*=7.37 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ_C: 11.56, 28.25, 34.91, 45.48, 120.54, 126.37, 126.68, 126.92, 127.02, 128.84, 134.13, 138.03, 147.39, 157.54, 162.25 (C=O). MS (*m/z*, %): 278 (M^+, 53.6), 174 (67.1), 105 (44.3), 77 (55.5). Anal. Calcd for: $C_{18}H_{18}N_2O$: C, 77.69; H, 6.47; N, 10.07; Found: C, 77.68; H, 6.50; N, 10.07.

2-Propyl-3-phenylethyl-4(3H)quinazolinone **(5r):** white crystals, m.p. 105–106 °C. IR (KBr), (ν_{max} /cm^{-1}): 1670 (C=O). ^{1}H NMR (CDCl$_3$) δ_H: 1.49 (t, *J*=7.37 Hz, 3H, CH_3), 2.28 (m, 2H, CH_2), 3.50 (t, *J*=7.76 Hz, 2H, CH_2), 4.74 (t, *J*=7.76 Hz, CH_2, 2H), 7.70-8.17 (m, 8H), 8.75 (dd, *J*=0.91 Hz, *J*=7.05 Hz, 1H). ^{13}C NMR (CDCl$_3$) δ_C: 13.95, 20.66, 34.92, 36.87, 45.57, 120.52, 126.28, 126.63, 126.89, 126.98, 128.83, 134.o7, 138.08, 147.36, 156.59, 162.17(C=O). MS (*m/z*, %): 292 (M+, 45.2), 119 (32.4), 105 (42.5), 93 (39.5), 77 (62.5). Anal. Calcd for $C_{19}H_{20}N_2O$: C, 78.08; H, 6.84; N, 9.58; Found: C, 78.06; H, 6.84; N, 9.53.

2-Butyl-3-phenylethyl-4(3H)quinazolinone **(5s):** white crystals, m.p. 109–110 °C. IR (KBr), (ν_{max} /cm^{-1}): 1680 (C=O). ^{1}H NMR (CDCl$_3$) δ_H: 1.45 (t, *J*=7.37, 3H, CH_3), 1.91 (m, 2H, CH_2), 2.5 (m, 2H, CH_2), 3.13 (t, *J*=7.7 Hz, 2H, CH_2), 3.53 (t, *J*=7.64 Hz, 2H, CH_2), 4.77 (t, *J*=7.64 Hz, 2H, CH_2), 7.72–8.20 (m, 8H), 8.87 (dd, *J*=1.38 Hz, *J*=6.59 Hz, 1H). ^{13}C NMR (CDCl$_3$) δ_C: 13.88, 22.58, 29.47, 34.85, 34.98, 45.66, 120.51, 126.31, 126.67, 126.92, 126.96, 128.85, 134.11, 138.08, 147.39, 156.93, 162.23 (C=O). MS (*m/z*, %): 306 (M$^+$, 47.5), 264 (21.4), 105(36.5), 119 (40.2), 93 (20.1), 77 (46.5). Anal. Calcd for $C_{20}H_{22}N_2O$: C, 78.43; H, 7.20; N, 9.16; Found: C, 78.47; H, 7.23; N, 9.15.

2-Phenyl-3-phenylethyl-4(3H)quinazolinone **(5t):** white powdery crystals, m.p. 175–176 °C. IR (KBr), (ν_{max} /cm^{-1}): 1667 (C=O). ^{1}H NMR (CDCl$_3$) δ_H: 3.42, (t, *J*=7.85 Hz, 2H, CH_2), 4.70 (t, *J*=7.85 Hz, 2H, CH_2), 7.37-8.28 (m, 13H), 8.87 (dd, *J*=0.68 Hz, *J*=7.56 Hz, 1H). ^{13}C NMR (CDCl$_3$) δ_C: 34.75, 47.59, 120.99, 126.69, 126.78, 127.11, 127.58, 127.84, 128.63, 128.81, 129.86, 134.44, 135.40, 137.80, 147.21, 156.17, 162.15 (C=O). MS (*m/z*, %): 326 (M$^+$, 38.2), 222 (81.3), 119 (58.5), 105 (37.2), 93 (41.5), 77 (56.4), 51 (24.4). Anal. Calcd for $C_{22}H_{18}N_2O$: C, 80.85; H, 5.55; N, 8.58; Found: C, 80.75; H, 5.52; N, 8.51.

We are grateful to the Shahid Beheshti University Research Council for financial support of this work.

Received 24 February 2004; accepted 7 June 2004
Paper 04/2357

References

1 For recent reviews see: P. Laszlo, *Acc. Chem. Res*., 1996, **19**, 121; A. Cornelis and P. Laszlo, *Synlett*, 1994, 155; M, Balogh and P. Laszlo, *Organic Chemistry Using Clays*. Springer Verlag, NewYork, 1993.
2 For recent reviews see: T.S. Jin, *Chin. J. Org. Chem*., 1996, **16**, 385; B. Perio, M.J. Dozias, P. Jacquault and J. Hamelin, *Tetrahedron Lett*., 1997, **38**, 7867; S. Jolivet-Fauchet, J. Hamelin, F.Texier-Boullet, L. Toupet and P. Jacquault, *Tetrahedron*, 1998, **54**, 4561; K. Toshima, Y. Ushilci, G. Matsuo and S. Matsumura, *Tetrahedron Lett*., 1997, **38**, 7375.
3 R.A. Abramovitch, *Org. Prep. Proc. Int*., 1991, **23**, 683; D.M.P. Mingos and D.R. Baghurst, *Chem. Soc. Rev*., 1991, **20**, 1-47; S. Caddick, Tetrahedron, 1995, **51**, 10403; C.R. Strauss and R. W. Trainer, *Aust. J. Chem*., 1995, **48**, 1665. For a review see: P. Lidström, J. Tierney, B.Wathey, and J. Westman, *Tetrahedron*, 2001, **57**, 9225; A. Loupy, A. Petit. J. Hamelin, F. Texier- Boullet, P. Jacquault and D. Mathe, *Synthesis*, 1998, 1213.
4 L. Deloude and P. Laszlo, *J. Org. Chem*., 1996, **61**, 6360; R.S. Varma and R. Dehiya, *Synlett*, 1997, 857; R.S. Varma and H.M. Meshram, *Tetrahedron Lett*., 1997, **38**, 7973.
5 A.M.M.E Omar, S.A.S. El-Din,I. M. Labouta, and A.A. El-Tambary, *Alexandria J. Pharm. Sci*., 1991, **5**, 94 (*Chem. Abstr.*, 1992, **116**, 55402b).
6 D.J. Baek, Y.K. Park, H.I. Heo, M.H. Lee, Z.Y. Yang and M.H. Choi, *Bioorg. Med. Chem. Lett*., 1998, **8**, 3287.
7 V. Niementowski, *J. Prakt. Chem*., 1895, **51**, 546.
8 S. Makino, N. Suzuki, E. Nakanishi and T. Tsuji, *Synlett*., 2000, 1670.
9 J.P. Mayer, G.S. Lewis, M.J. Curtis and J.W. Zhang, *Tetrahedron Lett*., 1997, **38**, 8445.
10 R.Y. Yang and A. Kaplan, *Tetrahedron Lett*., 2000, **41**, 7005.
11 M.J. Deetz, J.P. Malerich, A.M. Beatty and B.D. Smith, *Tetrahedron Lett.*, 2001, **42**, 1851.
12 F-R. Alexander, A. Berecibar, R. Wrigglesworth and T. Besson, *Tetrahedron*, 2003, **59**, 1413; J.S. Yadav and B.V.S. Reddy, *Tetrahedron Lett.*, 2002, **43**, 1905; H. Hazarkhani and B. Karimi, *Tetrahedron*, 2003, **59**, 4757.
13 R.H. Clark and E.C. Wagner, *J. Org. Chem*., 1944, **9**, 55.
14 H.W. Grimmel, A. Guenther and J.F. Morgan, *J. Am. Chem. Soc*., 1946, **68**, 542.
15 R. Andrisano and A. Chiesi, *Ateneo Parmense*, 1961, **32**, 671. (*Chem. Abstr.*, 1963, **58**, 3428c).
16 G. Rabilloud and B. Sillion, *J. Heterocyclic. Chem*., 1980, **17**, 1065.
17 T. Kato, A. Takada and T. Ueda, *Chem. Pharm. Bull*., 1976, **24**, 431.
18 G.B. Jackman, V. Petrow, and O. Stephenson, *J. Pharm. Pharmacol*., 1960, 529.
19 P.R. Levy and H. Stephen, *J. Chem. Soc*., 1956, 985.
20 M. Al-Talib, J.C. Jochims, A. Hamed, Q. Wang, and A. El-Hamid Ismail, *Synthesis*., 1992, 697.
21 M. Akazome, T. Kondo and Y. Watanabe, *J. Org. Chem*., 1993, **58**, 310.
22 L.A. Errede, J.J. McBrady and H. T. Oien, *J. Org. Chem*., 1977, **42**, 656.