Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 4757–4760

TETRAHEDRON

A facile synthesis of new 3-(2-benzimidazolyl)-2-alkyl-4-(3*H*)-quinazolinones under microwave irradiation

Hassan Hazarkhani* and Babak Karimi

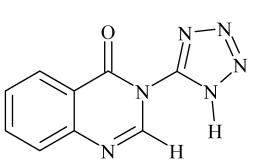
Department of Chemistry, Institute for Advanced Studies in Basic Sciences (IASBS), P.O. Box 45195-159, Gava Zang, Zanjan, Iran

Received 17 February 2003; revised 7 April 2003; accepted 1 May 2003

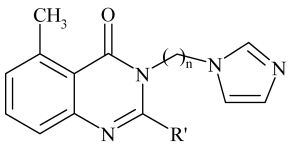
Abstract—Preparation of 2-amino-*N*-(1-*H*-benzimidazol-2-yl)benzamide and a variety of new 3-(2-benzimidazolyl)-2-alkyl-4-(3*H*)-quinazolinones using isatoic anhydride, 2-aminobenzimidazole and orthoesters under microwave irradiation are described.

One of the most frequently encountered heterocycles in medicinal chemistry is 4(3*H*)-quinazolinone with wide applications including anticonvulsant,[1] antihypertensive,[2] antidiabetic,[3] antibacterial,[4] antitumor,[5] antihistaminic,[6] and antiinflammatory[7] activities. On the other hand heterocyclic molecules containing benzimidazole groups is the another heterocyclic compounds that have been exhibiting a broad spectrum of pharmacological activities.[8] Important clinical examples of these heterocycles include mebendazole,[9] albendazole,[10] astemizole,[11] and omeprazole.[12] Recent investigations on biological activity of heterocycles containing benzimidazole ring clearly show that they play an important role as selective neuropeptide YY1 receptor antagonists,[13] factor Xa (FXa) inhibitors,[14] 5-lipoxygenase inhibitors for use as novel antiallergic agents,[15] poly(ADP-ribose) polymerase (PARP) inhibitors[16] and as human cytomegalovirus (HCMV) inhibitors.[17] Furthermore, a literature search shows that the study of polyheterocyclic systems based on a quinazolinone structural block has attracted intrest, owing to their potential useful biological activities. For example, 3-(1*H*-tetrazol-5-yl)-4(3*H*)-quinazolinone sodium salt (MDL 427, **A**) and 3-*N*-[(1*H*-imidazole-1-yl) alkyl]-4(3*H*)-quinazolinone (**B**) have been introduced as antiallergic and antihypertensive agents, respectively.[18]

Microwave irradiation has been extensively used for the rapid synthesis of a variety of heterocyclic compounds.[19] Very recently, we reported a facile synthesis of new 6-alkyl benzimidazo[1,2-*c*]quinazolines using isatoic anhydride and 2-(*o*-aminophenyl)benzimidazole under microwave irradiation in *N*,*N*-dimethyl acetamide (DMAC).[20]



A



R' = alkyl, n = 4, 5, 6

B

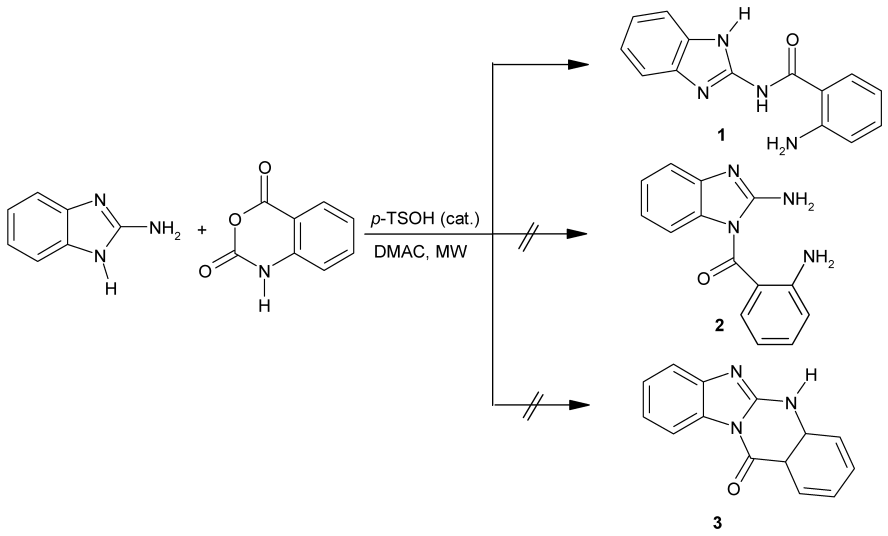
Along this line we have designed the synthesis of 3-(2-benzimidazolyl)-2-alkyl-4(3*H*)-quinazolinones as new heterocyclic compounds that contain both benzimidazole and quinazolinone moieties in their structures. These results encouraged us to prepare new polyheterocyclic systems, which bear two or three different heterocyclic nuclei. For this purpose, we have started from isatoic anhydride as a useful starting material that its applications in synthesis of heterocycles have been well documented.[21]

When a mixture of isatoic anhydride and 2-aminobenzimidazole in DMAC was irradiated with microwave (300 W power) in the presence of a catalytic amount of *p*-toluenesulfonic acid, the reaction was almost completed within 2 min. Work-up of the reaction mixture shows that 2-amino-*N*-(1-*H*-benzimidazol-2-yl)benzamide (**1**) was prepared in 70% yield after recrystallization from 95% ethanol (Scheme 1). Interestingly, we have found that this reaction is highly chemoselective in the preparation of amide **1**, since no detectable of either amides **3** or **4** is formed under the described reaction conditions.

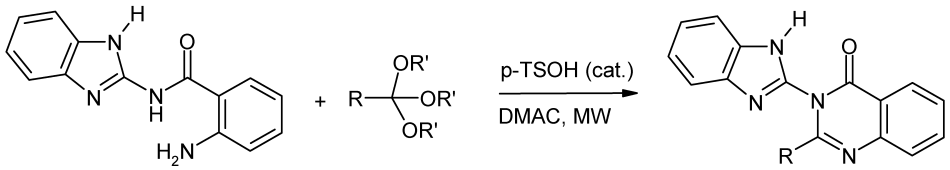
This new amide has three nucleophilic sites that can be condensed with different electrophilic species for preparation of a wide variety of quinazolinone based targets. Herein, we wish to report the synthesis of 3-(2-benzimida-

* Corresponding author. Tel.: +98-241-4242235; fax: +98-241-4248013; e-mail: hazarkhani@iasbs.ac.ir

0040–4020/03/$ - see front matter
doi:10.1016/S0040-4020(03)00696-3



Scheme 1.



Scheme 2.

zolyl)-2-alkyl-4-(3*H*)-quinazolinones through the reaction of **1** with a set of orthoesters under microwave irradiation. We have carried out the reaction of 2-amino-*N*-benzimidazolyl benzamide (**1**) with triethylorthoformate under microwave irradiations. For this purpose a mixture of the amide (5 mmol), triethylorthoformate (7.5 mmol), *p*-toluenesulfonic acid (0.25 mmol) and DMAC (1–2 ml) in a tall beaker was covered with a stemless funnel and placed in a microwave oven and irradiated with 600 W power for 4 min (irradiation sequences were interrupted with a cooling period in between). Then the reaction mixture was allowed to cool to room temperature and poured in a large volume of cool water to give precipitate.

The precipitate was filtered off and recrystallized from ethanol (95%) to afford pure 3-benzimidazolyl-4(3*H*)-quinazolinone (**4a**) in 94% yield (Scheme 2). Reaction of 2-amino-*N*-(1-*H*-benzimidazol-2-yl)benzamide (**1**) with triethyl orthoacetate, triethyl orthopropionate, trimethyl orthobutyrate and trimethyl orthovalerate under similar reaction conditions gave the 2-methyl, 2-ethyl, 2-propyl and 2-butyl-3-benzimidazolyl-4(3*H*)-quinazolinones (**4b**-**e**) in high yields, respectively (Scheme 2). The work on the preparation of other types of substituted quinazolinones and the study of their biological activities are on going in our laboratories.

In summary we have reported a facile, rapid and useful synthesis of new substituted quinazolinones under microwave irradiation. The yield of reactions is high and work up of the product is easy.

1. Experimental

1.1. Typical procedure for preparation of 2-amino-*N*-(1-*H*-benzimidazol-2-yl)benzamide (1)

A mixture of isatoic anhydride (1.63 g, 10 mmol), 2-aminobenzimidazole (1.35 g, 10 mmol), *p*-toluenesulfonic acid (0.05 g, 0.25 mmol) and *N*,*N*-dimethylacetamide (DMAC, 1–2 ml) in a tall beaker was covered with stemless funnel, placed in microwave oven and irradiated with 300 W power for 30 s (evolution of CO_2 was observed). The reaction mixture was cooled and irradiated again for 90 s with interruptions in between. Then, the reaction mixture was allowed to cool to room temperature and poured in cool water (250 ml). The precipitate formed was filtered and washed with water. Recrystallization from ethanol (95%) gave 2-amino-*N*-benzimidazolyl benzamide (**1**) as white crystals, 1.76 g, 70%, mp 220–2°C.

1.2. General procedure for preparation of 3-(2-benzimidazolyl)-2-alkyl-4(3*H*)-quinazolinones (4a-e)

A mixture of 2-amino-*N*-benzimidazolyl benzamide (**1**) (1.26 g, 5 mmol), orthoester (7.5 mmol), *p*-toluenesulfonic acid (0.05 g, 0.25 mmol) and *N*,*N*-dimethylacetamide (DMAC, 1–2 ml) in a tall beaker was covered with stemless funnel, placed in microwave oven and irradiated with 600 W power for 30 s. The reaction mixture was cooled and irradiated again for 4–5 min with interruptions in between. Then, the reaction mixture was allowed to cool to room temperature and poured into cool water (250 ml). The

precipitates formed were filtered and washed with water. Recrystallization from 95% ethanol or absolute ethanol gave 3-(2-benzimidazolyl)-2-alkyl-4(3*H*)-quinazolinones in good to high yields.

1.3. Spectral data

1.3.1. 2-Amino-*N*-benzimidazolyl benzamide (1). From 95% ethanol, mp 220–2°C. IR (KBr) ν 3337 (broad), 3190, 3063, 2967, 2878, 1645, 1606, 1575, 1525, 1421, 1348, 1278, 1228, 1163, 1020, 916, 881, 858, 746, 693 cm^{-1}. ^1H NMR (DMSO-d_6, 500 MHz) δ 12.01 (broad s, 2H), 7.95–7.93 (d, 1H, J=8.0 Hz), 7.43–7.40 (m, 2H), 7.19–7.16 (m, 1H), 7.12–7.10 (m, 2H), 6.80–6.77 (broad s, 2H), 6.75–6.73 (d, 1H, J=8.3 Hz), 6.54–6.51 (t, 1H, J=7.5 Hz) ppm. ^{13}C NMR (DMSO-d_6, 125 MHz) δ 172.23, 151.15, 150.20, 133.93, 133.08, 130.72, 122.09, 117.02, 115.42, 115.07, 113.32 ppm. MS (20 eV) *m*/*z* (relative intensity): 252 (M^+, 37.3), 236 (35.4), 134 (14.6), 120 (100), 92 (60.2), 65 (45.8). CHN analysis: %C (calcd 66.66, found 66.21), %H (calcd 4.79, found 4.78), %N (calcd 22.21, found 21.85).

1.3.2. 3-(2-Benzimidazolyl)-4(3*H*)-quinazolinone (4a). 1.23 g, 94%, from 95% ethanol, mp 300–2°C. IR (KBr) ν 3383–3229 (broad), 3071, 1691, 1622, 1510, 1440, 1386, 1259, 901, 760, 743 cm^{-1}. ^1H NMR (DMSO-d_6, 500 MHz) δ 13.06 (s, 1H), 9.02 (s, 1H), 8.34–8.33 (d, 1H, J=7.8 Hz), 7.98–7.95 (t, 1H, J=7.5 Hz), 7.83–7.81 (d, 1H, J=8.0 Hz), 7.71–7.68 (t, 2H, J=7.2 Hz), 7.65–7.64 (d, 1H, J=7.3 Hz), 7.30–7.27 (t, 2H, J=7.5 Hz). ^{13}C NMR (DMSO-d_6, 125 MHz) δ 160.25, 147.56, 144.87, 144.48, 141.05, 136.46, 134.49, 129.14, 128.54, 127.57, 123.84, 123.06, 122.09, 119.55, 113.46 ppm. MS (20 eV) *m*/*z* (relative intensity): 262 (M^+, 100), 234 (80.5), 134 (10.6), 118 (12.2), 102 (10.5), 76 (11.8), 50 (15.6). CHN analysis: %C (calcd 68.69, found 68.45), %H (calcd 3.84, found 3.80), %N (calcd 21.36, found 21.42).

1.3.3. 3-(2-Benzimidazolyl)-2-methyl-4(3*H*)-quinazolinone (4b). 1.31 g, 95%, from absolute ethanol, mp 237–9°C. IR (KBr) ν 3295 (broad), 3040, 2994, 1668, 1620, 1571, 1487, 1410, 1394, 1336, 1275, 959, 758, 746, 696 cm^{-1}. ^1H NMR (DMSO-d_6, 500 MHz) δ 8.50–8.48 (d, 1H, J=8.2 Hz), 8.24–8.23 (d, 1H, J=7.8 Hz), 7.49–7.44 (m, 3H), 7.23–7.21 (m, 2H), 7.13–7.10 (t, 1H, J=7.5 Hz), 3.39 (s, 1H), 2.75 (s, 3H). ^{13}C NMR (DMSO-d_6, 125 MHz) δ 174.09, 169.07, 152.41, 140.72, 132.68, 131.59, 130.96, 124.32, 123.53, 122.94, 120.51, 112.82, 26.08 ppm. MS (20 eV) *m*/*z* (relative intensity): 276 (M^+, 37.3), 162 (25.4), 133 (100), 119 (40.2), 92 (28.2), 76 (31.8), 43 (60.5). CHN analysis: %C (calcd 69.55, found 69.25), %H (calcd 4.38, found 4.35), %N (calcd 20.28, found 20.01).

1.3.4. 3-(2-Benzimidazolyl)-2-ethyl-4(3*H*)-quinazolinone (4c). 1.30 g, 90%, from absolute ethanol, mp 137–9°C. IR (KBr) ν 3584–3056 (broad), 2978–2932, 1695, 1656, 1598, 1575, 1529, 1496, 1348, 1275, 743 cm^{-1}. ^1H NMR (DMSO-d_6, 500 MHz) δ 12.60 (broad s, 1H), 8.18–8.16 (d, 1H, J=7.5 Hz), 7.91–7.88 (t, 1H, J=7.3 Hz), 7.76–7.74 (d, 1H, J=8.0 Hz), 7.70 (m, 2H), 7.59–7.56 (t, 1H, J=7.3 Hz), 7.31 (m, 2H), 2.48–2.46 (q, 2H, J=7.1 Hz), 1.17–1.14 (t, 3H, J=7.1 Hz) ppm. ^{13}C NMR (DMSO-d_6, 125 MHz) δ 161.86, 157.45, 147.45, 143.06, 141.05, 136.06, 127.88, 127.83, 127.06, 126.91, 123.24, 120.14, 27.99, 11.13 ppm. MS (20 eV) *m*/*z* (relative intensity): 290 (M^+, 37.3), 261 (12.2), 235 (42.1), 176 (24.2), 133 (100), 119 (40.2), 92 (18.5), 76 (22.8), 57 (15.6). CHN analysis: %C (calcd 70.33, found 70.01), %H (calcd 4.80, found 4.80), %N (calcd 19.30, found 18.95).

1.3.5. 3-(2-Benzimidazolyl)-2-propyl-4(3*H*)-quinazolinone (4d). 1.14 g, 75%, from absolute ethanol, mp 211–14°C. IR (KBr) ν 3306–3171 (broad), 2959, 2932, 2867, 1687, 1668, 1608, 1533, 1460, 1433, 1275, 770 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz) δ 11.29 (broad s, 1H), 7.67–7.47 (m, 4H), 7.22–7.12 (broad s, 2H), 6.99–6.98 (m, 2H), 2.43–2.40 (t, 2H, J=7.5 Hz), 1.75–1.71 (quartet, 2H, J=7.5 Hz), 0.85–0.82 (t., 3H, J=7.3 Hz) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz) δ 163.10, 156.19, 147.18, 141.97, 141.34, 135.44, 133.47, 127.25, 127.05, 125.82, 124.20, 123.26, 119.62, 118.87, 112.17, 34.45, 28.83, 22.26, 13.91 ppm. MS (20 eV) *m*/*z* (relative intensity): 304 (M^+, 47.3), 276 (28.4), 261 (22.5), 235 (20.3), 176 (20.5), 133 (100), 119 (40.2), 92 (15.8), 76 (45.8), 57 (16.5). CHN analysis: %C (calcd 71.04, found 70.85), %H (calcd 5.30, found 5.29), %N (calcd 18.41, found 18.01).

1.3.6. 3-(2-Benzimidazolyl)-2-butyl-4(3*H*)-quinazolinone (4e). 1.10 g, 70%, from absolute ethanol, mp 226.228°C. IR (KBr) ν 3325–3167 (broad), 2951, 2936, 2871, 1691, 1664, 1610, 1537, 1460, 1437, 1275, 770 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz) δ 11.50 (broad s, 1H), 7.56–7.49 (m, 4H), 7.13 (broad s, 2H), 7.06–7.03 (t, 2H), 2.53–2.50 (t, 2H, J=7.7 Hz), 1.73–1.67 (quintet, 2H, J=7.5 Hz), 1.26–1.19 (sex. 2H, J=7.5 Hz), 0.78–0.75 (t, 3H, J=7.25 Hz) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz) δ 163.24, 156.23, 147.24, 141.93, 135.29, 127.29, 126.99, 125.88, 124.09, 123.48, 119.80, 119.02, 34.44, 28.85, 22.19, 13.70 ppm. MS (20 eV) *m*/*z* (relative intensity): 318 (M^+, 47.3), 290 (15.5), 261 (25.6), 235 (22.4), 176 (15.8), 133 (14.6), 119 (40.2), 92 (20.1), 76 (45.8). CHN analysis: %C (calcd 71.68, found 71.30), %H (calcd 5.70, found 5.45), %N (calcd 17.60, found 17.23).

Acknowledgements

The authors are grateful to Institute for Advanced Studies in Basic Sciences (IASBS) for partial support of this work.

References

1. (a) Mannschreck, A.; Koller, H.; Stuhler, G.; Davies, M. A.; Traber, J. *Eur. J. Med. Chem.* **1984**, *19*, 381. (b) Gupta, C. M.; Bhaduri, A. P.; Khanna, N. M. *J. Med. Chem.* **1968**, *11*, 392.
2. (a) Hess, H. J.; Cronin, T. H.; Scriabine, A. *J. Med. Chem.* **1968**, *11*, 130. (b) Hussain, M. A.; Chiu, A. T.; Price, W. A.; Timmermans, P. B.; Shefter, E. *Pharm. Res.* **1988**, *5*, 242.
3. Malamas, M. S.; Millen, J. *J. Med. Chem.* **1991**, *34*, 1492.
4. Kung, P. P.; Casper, M. D.; Cook, K. L.; Wilson-Lin-gardo, L. *J. Med. Chem.* **1999**, *42*, 4705.
5. (a) Baek, D. J.; Park, Y. K.; Heo, H. I.; Lee, M.; Yang, Z.; Choi, M. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3287. (b) Webber, S. E.; Bleckman, T. M.; Attard, J.; Deal, J. G.; Kathardekar,

V.; Welsh, K. M.; Webber, S.; Janson, C.; Matthews, D. A.; Smith, W. W.; Freer, S. T.; Jordan, S. R.; Bacquet, R. J.; Howland, E. F.; Booth, C. L. J.; Ward, R. W.; Hermann, S. M.; White, J.; Morse, C. A.; Hilliard, J. A.; Bartlett, C. A. *J. Med. Chem.* **1993**, *36*, 733.
6. Omar, A. M. E.; El-Din, S. A. S.; Labouta, I. M.; El-Tambary, A. A.; Alexandria, J. *Pharm. Sci.* **1991**, *5*, 94.
7. Chao, Q.; Deng, L.; Shih, H.; Leoni, L. M.; Genini, D.; Carson, D. A.; Cottam, H. B. *J. Med. Chem.* **1999**, *42*, 3860.
8. Nawrocka, W. *Boll. Chim. Farm.* **1996**, *135*, 18.
9. Winstanley, P. *Lancet* **1998**, *352*, 1080.
10. Carpio, A. *J. Neurol. Neurosurg. Psychiat.* **1999**, *66*, 411.
11. Al-Muhaimeed, H. *J. Int. Med. Res.* **1997**, *25*, 175.
12. Richter, J. E. *Am. J. Gastroenterol.* **1997**, *92*, 34.
13. Zarrinmayeh, H.; Nunes, A. M.; Ornstein, P. L.; Zimmerman, D. M.; Arnold, M. B.; Schober, D. A.; Gackenheimer, S. L.; Bruns, R. F.; Hipskind, P. A.; Britton, T. C.; Cantrell, D. R. *J. Med. Chem.* **1998**, *41*, 2709.
14. Nakano, H.; Inoue, T.; Kawasaki, N.; Miyataka, H.; Matsumoto, H.; Taguchi, T.; Inagaki, N.; Nagai, H.; Satoh, T. *Bioorg. Med. Chem.* **2000**, *8*, 373.
15. Zhao, Z. S.; Arnaiz, D. O.; Griedel, B.; Sakata, S.; Dallas, J. L.; Whitlow, M.; Trinh, L.; Post, J.; Liang, A.; Morrissey, M. M.; Shaw, K. J. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 963.
16. White, A. W.; Almassy, R.; Calvert, A. H.; Curtin, N. J.; Griffin, R. J.; Hostomsky, Z.; Maegley, K.; Newell, D. R.; Srinivasan, S.; Golding, B. T. *J. Med. Chem.* **2000**, *43*, 4084.
17. Zhu, Z.; Lippa, B.; Drach, J. C.; Townsend, L. B. *J. Med. Chem.* **2000**, *43*, 2430.
18. (a) William, B. W.; Andrew, S. T. Jr.; Peter, S. C.; Joseph, W. M.; Jeffery, B. P. *J. Med. Chem.* **1987**, *30*, 2277. (b) Cross, P. E.; Dickinson, R. P.; Parry, M. J.; Randall, M. J. *J. Med. Chem.* **1985**, *28*, 1427. (c) Norton, P. P.; Larry, E. B.; Shyam, S.; Jon, E. L.; Emily, H. M.; Edward, L. O. *J. Med. Chem.* **1986**, *29*, 2403.
19. For a review see: (a) Lidström, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225. (b) Rad-Moghadam, K.; Khajavi, M. S. *J. Chem. Res. (S)* **1998**, 702. (c) Khajavi, M. S.; Mohammadi, A. A.; Sadat Hosseini, S. S. *Synth. Commun.* **2001**, *31*, 3647.
20. Khajavi, M. S.; Rad-Moghadam, K.; Hazarkhani, H. *Synth. Commun.* **1999**, *29*, 2617.
21. For a review of chemistry of isatoic anhydride see: Coppola, G. M. *Synthesis* **1980**, 505.