ACADEMIA ROMÂNĂ
Revue Roumaine de Chimie
http://web.icf.ro/rrch/

Rev. Roum. Chim.,
2014, *59*(2), 147-150

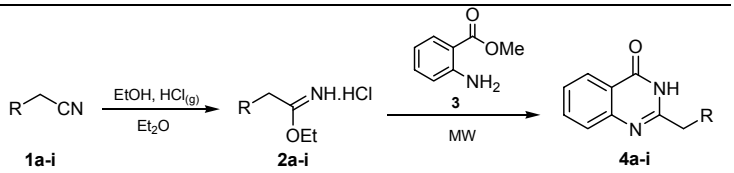
MICROWAVE-ASSISTED SYNTHESIS OF SOME 2-SUBSTITUTED QUINAZOLIN-4(3H)-ONE DERIVATIVES FROM IMINOESTER HYDROCHLORIDES

Emre MENTEŞE[a,*] and Bahittin KAHVECİ[b]

[a] Department of Chemistry, Art and Science Faculty, Recep Tayyip Erdoğan University, Rize, Turkey
[b] Department of Nutrition and Dietetics, Faculty of Health Sciences, Karadeniz Technical University, Trabzon, Turkey

Received January 30, 2014

Herein, a method that involves a reaction of iminoester hydrochloride with methyl anthranilate via microwave assisted synthesis is reported. This efficient procedure provides pure products within few minutes. This method can be used as a general technique for synthesizing quinazoline derivatives.



INTRODUCTION

Traditionally, heterocyclic synthesis is carried out by conductive heating with an oil bath or heating mantle. It is a comparatively slow and inefficient method for transferring energy into reaction system. In addition, a temperature gradient can develop in the sample and local overheating can lead to product, substrate or reagent decomposition. In contrast, microwave heating produces efficient internal heating by direct coupling of microwave energy with the molecules in the reaction mixture. In this reason, not only is direct microwave heating able to reduce chemical reaction times, but it is also known to reduce side reactions, increase yields, and improve reproducibility. Nowadays, many organic reactions have been carried out by microwave heating. It is a unique technique for the synthetic organic chemists have synthesized a large number of new drugs by using microwave irradiation.[1-8]

Quinazolone and their derivatives are very important for medicinal chemistry because of the interesting biological properties such as antifungal, antitumor, antihypertensive, anticonvulsant, analgesic, antiinflammatory, anticonvulsant, antidiabetic, hypolipidemic, and protein tyrosine kinase inhibitors.[9-14] In addition, there are some drugs containing quinazolin moiety like Proquazone, Nolatrexed, Afloqualone, Linagliptin, Quinazolinone.[14, 15] They also are used in diverse areas of chemistry that are very important intermediates in pharmaceutical chemistry.[13]

There are several methods for the synthesis of 2-substituted quinazolin-4(3H)-one derivatives. The most common protocol for the synthesis of these type compounds involves a cyclocondensation reaction of 2-aminobenzoic acids or their derivatives with carboxylic acid derivatives under acidic or basic conditions.[16-19] Also, these type compounds are synthesized via microwave technique.[20, 21] In this work, an attemption has been made to synthesis of quinazolin derivatives by treating methyl anthranilate with iminoester hydrochlorides using microwave heating as an efficient method.

EXPERIMENTAL

All the chemicals were supplied by Merck (Darmstadt, Germany), Aldrich and Fluka (Buchs SG, Switzerland).

* Corresponding author: emre.mentese@erdogan.edu.tr, phone: +90 464 223 61 26, fax: +90 464 223 4019

Melting points were determined on capillary tubes on a Büchi oil-heated melting point apparatus (Essen, Germany) and uncorrected. ^{1}H-NMR and ^{13}C-NMR spectra were performed on the Varian-Mercury 400 MHz spectrometer (Varian, Darmstadt, Germany) in DMSO-d_6 using TMS as internal. Mass spectra were recorded on Thermo Scientific Quantum Access max LC- MS spectrophotometer. Elemental Analyses were performed on a Carla Erba 1106 CHN analyser (Heraeus, Hanau, Germany). A *Monomode CEM-Discover Microwave* instrument was used in the standard configuration as delivered, including proprietary software. All experiments were carried out in microwave process vials (30 mL) with infrared temperature control sensor. The temperature was computer monitored and maintained constant by a discrete modulation of delivered microwave power. After completion of the reaction, the vial was cooled to 60° by air jet cooling. All reactions were monitored by TLC using precoated aluminum sheets (silica gel 60 F 2.54 0.2 mm thickness).

Synthesis of Compounds 4a-i

A mixture of methyl anthranilate (**3**) (0.010 mol) and iminoester hydrochlorides (0.013 mol) (**2a-i**) in dry dioxane (15 mL) was irradiated in microwave at 35 ^{o}C for 10 min (hold time) at 100 W maximum power. Again, it was irradiated with the pressure control at 100-102 ^{o}C for 15 min (hold time) at 300 W maximum power. After the completion of the reaction (monitored by TLC, ethylacetate:hexane, 7:2), the mixture was evaporated to dryness at pressure. The residue was recrystallized from acetone-water (5:1) or ethylacetate-petroleum ether (3:1) to give pure **4a-i.**

2-(2-Bromobenzyl)quinazolin-4(3H)-one (**4a**):
Yield 45 %, mp: 220-222 °C, ^{1}H NMR (400 MHz, DMSO-d_6): δ= 4.01 (s, 2H, CH_2), 7.31-7.62 (m, 6H, Ar-H), 7.81-7.83 (m, 1H, Ar-H), 8.08-8.10 (m, 1H, Ar-H), 12.47 (s, 1H, NH). ^{13}C-NMR (100 MHz, DMSO-d_6): δ= 40.6 (CH_2), 110.6, 112.9, 116.1, 124.9, 127.9, 129.1, 131.6, 132.4, 135.1, 136.2, 149.6 (Ar-C), 154.9 (C=N), 169.8 (C=O). Anal. Calcd for $C_{15}H_{11}BrN_2O$: C, 57.16; H, 3.52; N, 8.89. Found: C, 57.22; H, 3.54; N, 8.85. LC-MS m/z: 316.26 $[M+1]^+$.

2-(3-Bromobenzyl)quinazolin-4(3H)-one (**4b**):
Yield 71 %, mp: 243-244 °C, ^{1}H NMR (400 MHz, DMSO-d_6): δ= 3.95 (s, 2H, CH_2), 7.28-7.62 (m, 6H, Ar-H), 7.75-7.80 (m, 1H, Ar-H), 8.07-8.09 (m, 1H, Ar-H), 12.41 (s, 1H, NH). ^{13}C-NMR (100 MHz, DMSO-d_6): δ= 40.7 (CH_2), 121.2, 122.1, 126.2, 126.8, 127.4, 128.5, 130.2, 131.1, 132.2, 134.9, 139.6, 149.2 (Ar-C), 155.9 (C=N), 162.3 (C=O). Anal. Calcd for $C_{15}H_{11}BrN_2O$: C, 57.16; H, 3.52; N, 8.89. Found: C, 57.21; H, 3.55; N, 8.86. LC-MS m/z: 314.98 $[M]^+$, 316.26 $[M+2]^+$.

2-(2-Florobenzyl)quinazolin-4(3H)-one (**4c**):
Yield 70 %, mp: 242-243 °C, ^{1}H NMR (400 MHz, DMSO-d_6): δ= 4.02 (s, 2H, CH_2), 7.11-7.73 (m, 6H, Ar-H), 7.75-7.77 (m, 1H, Ar-H), 8.08-8.10 (m, 1H, Ar-H), 12.44 (s, 1H, NH). ^{13}C-NMR (100 MHz, DMSO-d_6): δ= 34.4 (d, $J_{C,F}$= 3 Hz, CH_2), 115.6 (d, $J_{C,F}$= 21 Hz), 121.3, 123.7, 124.5, 126.2, 126.7, 127.4, 128.9, 129.5, 131.8, 132.3 (d, $J_{C,F}$= 3 Hz), 134.8, 149.2 (Ar-C), 155.4 (C=N), 160.9 (d, $J_{C,F}$= 243 Hz, C-F), 162.2 (C=O). Anal. Calcd for $C_{15}H_{11}FN_2O$: C, 70.86; H, 4.36; N, 11.02. Found: C, 70.90; H, 4.39; N, 10.99. LC-MS m/z: 254.90 $[M]^+$, 255.88 $[M+1]^+$.

2-(4-Florobenzyl)quinazolin-4(3H)-one (**4d**):
Yield 45 %, mp: 225-227 °C,[17] ^{1}H NMR (400 MHz, DMSO-d_6): δ= 3.96 (s, 2H, CH_2), 7.17-7.48 (m, 5H, Ar-H), 7.63 (d, *J*= 7.9 Hz, 1H, Ar-H), 7.75-7.80 (m, 1H, Ar-H), 8.06-8.09 (m, 1H, Ar-H), 12.44 (s, 1H, NH). ^{13}C-NMR (100 MHz, DMSO-d_6): δ= 40.1 (CH_2), 115.3 (d, $J_{C,F}$= 21 Hz), 120.7, 125.8, 126.2, 126.9, 130.6, 132.5 (d, $J_{C,F}$= 3.5 Hz), 133.1, 148.8 (Ar-C), 155.8 (C=N), 161.4 (d, $J_{C,F}$= 240 Hz, C-F), 161.9 (C=O). Anal. Calcd for $C_{15}H_{11}FN_2O$: C, 70.86; H, 4.36; N, 11.02. Found: C, 70.91; H, 4.41; N, 10.98. LC-MS m/z: 255.04 $[M+1]^+$.

2-(4-Chlorobenzyl)quinazolin-4(3H)-one (**4e**):
Yield 47 %, mp: 241-243 °C,[17] ^{1}H NMR (400 MHz, DMSO-d_6): δ= 3.97 (s, 2H, CH_2), 7.40-7.48 (m, 5H, Ar-H), 7.58-7.62 (m, 1H, Ar-H), 7.74-7.77 (m, 1H, Ar-H), 8.09 (d, *J*= 7.6 Hz, 1H, Ar-H), 12.45 (s, 1H, NH). ^{13}C-NMR (100 MHz, DMSO-d_6): δ= 40.0 (CH_2), 120.7, 125.7, 126.3, 126.9, 128.4, 130.8, 134.4, 135.5, 148.8 (Ar-C), 155.6 (C=N), 161.8 (C=O). Anal. Calcd for $C_{15}H_{11}ClN_2O$: C, 66.55; H, 4.10; N, 10.35. Found: C, 66.58; H, 4.14; N, 10.33. LC-MS m/z: 270.06 $[M]^+$.

2-(4-Methylbenzyl)quinazolin-4(3H)-one (**4f**):
Yield 78 %, mp: 229-231 °C,[17] ^{1}H NMR (400 MHz, DMSO-d_6): δ= 2.77 (s, 3H, CH_3), 3.90 (s, 2H, CH_2), 7.09-7.28 (m, 4H, Ar-H), 7.41-7.63 (m, 2H, Ar-H), 7.78 (t, *J*= 8 Hz, 1H, Ar-H), 8.08 (d, *J*= 8 Hz, 1H, Ar-H), 12.43 (s, 1H, NH). ^{13}C-NMR (100 MHz, DMSO-d_6): δ= 21.1 (CH_3), 42.3 (CH_2), 121.2, 126.2, 126.7, 127.2, 129.2, 129.5, 133.9, 134.9, 135.6 (Ar-C), 156.8 (C=N), 162.3 (C=O). Anal. Calcd for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.19. Found: C, 76.83; H, 5.67; N, 11.14. LC-MS m/z: 250.89 $[M]^+$.

2-(2,4-Dichlorobenzyl)quinazolin-4(3H)-one (**4g**):
Yield 41 %, mp: 203-205 °C, ^{1}H NMR (400 MHz, DMSO-d_6): δ= 4.11 (s, 2H, CH_2), 7.14-7.55 (m, 4H, Ar-H), 7.60-7.75 (m, 2H, Ar-H), 8.10 (d, *J*= 8 Hz, 1H, Ar-H), 12.42 (s, 1H, NH). ^{13}C-NMR (100 MHz, DMSO-d_6): δ= 39.8 (CH_2), 126.2, 126.8, 127.8, 128.7, 129.1, 132.4, 133.5, 134.8, 135.1, 155.6 (C=N), 162.1 (C=O). Anal. Calcd for $C_{15}H_{10}Cl_2N_2O$: C, 59.04; H, 3.30; N, 9.18. Found: C, 59.11; H, 3.33; N, 9.15. LC-MS m/z: 304.99 $[M]^+$, 306.88 $[M+2]^+$, 308.77 $[M+4]^+$.

2-(3,4-Dichlorobenzyl)quinazolin-4(3H)-one (**4h**):
Yield 60 %, mp: 263-265 °C, ^{1}H NMR (400 MHz, DMSO-d_6): δ= 3.97 (s, 2H, CH_2), 7.37 (d, *J*= 1.6 Hz, 1H, Ar-H), 7.47 (t, *J*= 7.6 Hz, 1H, Ar-H), 7.59 (d, *J*= 8 Hz, 2H, Ar-H), 7.67 (s, 1H, Ar-H), 7.77 (t, *J*= 8 Hz, 1H, Ar-H), 8.08 (d, *J*= 7.6 Hz, 1H, Ar-H), 12.41 (s, 1H, NH). ^{13}C-NMR (100 MHz, DMSO-d_6): δ= 39.4 (CH_2), 121.3, 126.8, 127.4, 130.0, 131.3, 134.9, 137.9, 149.2, 155.6 (C=N), 162.3 (C=O). Anal. Calcd for $C_{15}H_{10}Cl_2N_2O$: C, 59.04; H, 3.30; N, 9.18. Found: C, 59.10; H, 3.33; N, 9.14. LC-MS m/z: 304.91 $[M]^+$, 306.80 $[M+2]^+$, 308.83 $[M+4]^+$.

2-(2,6-Dichlorobenzyl)quinazolin-4(3H)-one (**4i**):
Yield 20 %, mp: 254-256 °C, ^{1}H NMR (400 MHz, DMSO-d_6): δ= 3.98 (s, 2H, CH_2), 7.33-7.76 (m, 5H, Ar-H), 7.77-7.80 (m, 1H, Ar-H), 8.07-8.09 (m, 1H, Ar-H), 12.43 (s, 1H, NH). ^{13}C-NMR (100 MHz, DMSO-d_6): δ= 39.4 (CH_2), 120.3, 125.7, 126.2, 126.9, 128.0, 130.4, 131.4, 134.5, 137.9, 149.3, 155.5 (C=N), 162.2 (C=O). Anal. Calcd for $C_{15}H_{10}Cl_2N_2O$: C, 59.04; H, 3.30; N, 9.18. Found: C, 59.11; H, 3.34; N, 9.15. LC-MS m/z: 304.90 $[M]^+$, 306.81 $[M+2]^+$, 308.84 $[M+4]^+$.

Synthesis of Compounds 6

A mixture of methyl anthranilate (**3**) (0.020 mol) and compound **5** (0.014 mol) in dry dioxane (15 mL) was irradiated with microwave at 30 °C for 10 min, at 100 W

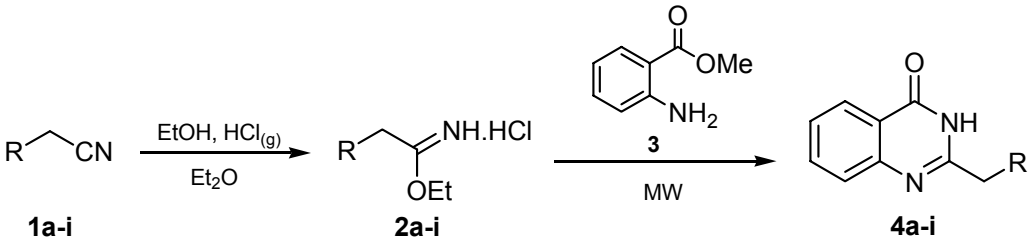
maximum power. Again, it was irradiated with the pressure control at 105 °C for 15 min (hold time) at 300 W maximum power. After the completion of the reaction (monitored by TLC, AcOEt/hexane, 7:2), the mixture was poured onto H_2O. The precipitate formed was filtered and recrystallized from ethylacetate- petroleum ether (3:1) to give pure compounds, **6.** Yield 70 %, mp: 297-299 °C, ^{1}H NMR (400 MHz, DMSO-d_6): δ= 4.06 (s, 4H, CH_2), 6.78-7.44 (m, 8H, Ar-H), 7.70-8.04 (m, 4H, Ar-H), 12.42 (s, 2H, NH). ^{13}C-NMR (100 MHz, DMSO-d_6): δ= 42.3 (CH_2), 115.2, 117.0, 126.1, 129.1, 129.7, 130.3, 132.8, 133.5, 134.5, 134.9, 149.4 (Ar-C), 155.9 (C=N), 162.3 (C=O). Anal. Calcd for $C_{24}H_{18}N_4O_2$: C, 73.08; H, 4.60; N, 14.20. Found: C, 73.14; H, 4.63; N, 14.15. LC-MS m/z: 394.28 $[M]^+$.

RESULTS AND DISCUSSION

As an extension to our previous studies on the development of microwave-assisted heterocyclic synthesis,[22-25] a far more effective and rapid method for the synthesis of quinazolin derivatives is reported in this study. Firstly, we synthesized iminoester hydrochlorides (**2a-i**, **5**) as a starting material using Pinner method.[26] A reaction of compound **3** with iminoester hydrochlorides (**2a-i**) in dioxane by microwave irradiation resulted to the compounds **4a-i**. Best yield was obtained at 100 °C in 15 minutes. We developed alternative protocol for the synthesis of 2-substituted quinazolin-4(3H)-one derivatives which are highly efficient, environmentally friendly, and less time consuming (Scheme 1). When using ethanol as a solvent, the reaction time decreases, but also the yield of the reaction decreases. It was noted that in the presence of electron-with drawing groups on the -orto and -para position of iminoester hydrochlorides reduces the yield of the reaction.

Bisquinazolin-4(3H)-one derivative also was obtained by the reaction of iminoester hydrochoride (**5**) with methyl anthranilate for the first time (Scheme 2).

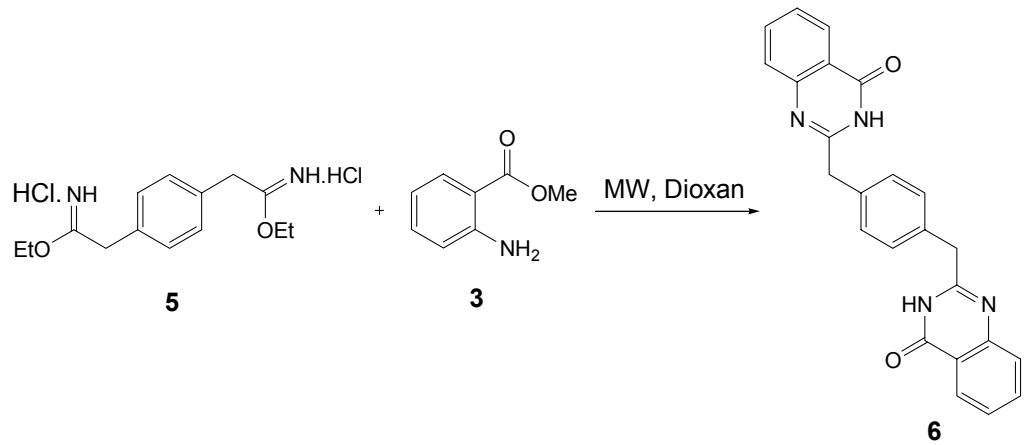
The structures of new compounds were confirmed by ^{1}H-NMR, ^{13}C-NMR spectroscopy, mass spectrometry and elemental analyses. Spectroscopic investigations of newly synthesized compounds are accordance with the proposed structure.



1a-i **2a-i** **4a-i**

	a	b	c	d	e
R	2-BrC_6H_4	3-BrC_6H_4	2-FC_6H_4	4-FC_6H_4	4-ClC_6H_4
	f	**g**	**h**	**i**	
R	4-MeC_6H_4	2,4-ClC_6H_4	3,4-ClC_6H_4	2,6-ClC_6H_4	

Scheme 1 – Synthetic route of compounds **4a-i**.



5 **3** **6**

Scheme 2 – Synthesize of bisquinazolin-4(3H)-one derivative (**6**).

CONCLUSIONS

In this work, we developed an efficient alternative method for the synthesis of quinazolin derivatives by using microwave irradiation starting from iminoester hydrochlorides. Also, bisquinazolin-4(3H)-one derivatives were synthesized from iminoester for the first time. This developed protocol can provide a suitable way for synthesizing new potentially bioactive quinazolin derivatives.

REFERENCES

1. E. Menteşe, M. Ozil, Ş. A. Karaoğlu and B. Kahveci, *J. Heterocyc. Chem.*, **2013**, *50*, 386-390.
2. C. O. Kappe, D. Dallinger and S. Murphree, "Practical microwave synthesis of organic chemists", Wilay VCH, Weinheim, 2009.
3. S. E. Wolkenberg, D. D. Wisnoski, W. H. Leister, Y. Wang, Z. Zhao and C.W. Lindsley, *Org. Lett.*, **2004**, *6*, 1453-1456.
4. M. P. Pospisil, *Heterocycles*, **2004**, *63*, 1165-1173.
5. H. Emtenas, C. Taflin and F. Almqvist, *Mol. Diversity*, **2003**, *7*, 165-169.
6. C. A. Suresh, B. P. Pinki, A. Rakshit and A. Chetna, "Microwave-Assisted Organic Synthesis: A Green Chemical Approach", Apple Academic Press, New Jersey, 2014.
7. F. Yılmaz and E. Menteşe, *Current Microwave Chemistry*, **2014**, *1*, 47-51.
8. A. Majumder, R. Gupta and A. Jain, *Green Chemistry Letters and Reviews*, **2013**, *6*, 151-182.
9. S. Boyapati, U. Kulandaivelu, S. Sangu and M. R. Vanga, *Arch. Pharm. Chem. Life Sci.*, **2010**, *10*, 570-576.
10. G.Grover and S. K. Kini, *Eur. J. Med. Chem.*, **2006**, *41*, 256-262.
11. J. Varsha, M. Pradeep, K. Sushil and J. P. Stables, *Eur. J. Med. Chem.*, **2008**, *43*, 135-141.
12. A. K.Tiwari, V. K. Singh, A. Bajpai, G. Shukla, S. Singh and A. K.Mishra, *Eur. J. Med. Chem.*, **2007**, *42*, 1234-1238.
13. T. P. Selvam and P. V. Kumar, *Res. Pharm.*, **2011**, *1*, 1-21.
14. T. Besson and E. Chosson, Comb. Chem. High Through. Screening, **2007**, *10*, 903–917.
15. R. Rajput and A. P. Mıshra, *Int. Pharm. and Pharmacol. Science*, **2012**, *4*, 66-70.
16. D. J. Connolly, D. Cusack, T. P. O'Sullivan and P. J. Guiry, *Tetrahedron*, **2005**, *61*, 10153-10202.
17. M. Adib, S. Ansari, A.Mohammadi and H. R. Bijanzadeh, *Tetrahedron Lett.*, **2010**, *51*, 30-32.
18. V. I. Kelarev, M. A. Silin, V. N. Koshelev and O. A. Borisova, *Chem. Heterocycl. Comp.*, **2004**, *40(5)*, 616-621.
19. A. V. Bogolubsky, S. V. Ryabukhin, A. S. Plaskon, S. V. Stetsenko, D. M. Volochnyuk and A. A. Tolmachev, *J. Comb. Chem.*, **2008**, *10*, 858-862.
20. M.Bakavoli, O. Sabzevari and M. Rahimizadeh, *Chinese Chem. Lett.*, **2007**, *18*, 1466-1468.
21. F. Li, Y. Feng, Q. Meng, W. Li, Z. Li, Q. Wang and F. Tao, *Arkivoc*, **2007**, *(i)*, 40-50.
22. E. Menteşe, H. Bektaş, S. Ülker, O. Bekircan and B. Kahveci, *Enzym Inh. and Med. Chem.*, **2014**, *29*, 64-68.
23. B. Kahveci, F.Yılmaz, E. Menteşe and F. Ş. Beriş, *J. Chem. Res.*, **2012**, *8*, 484-488.
24. E. Menteşe, N. Karaali, F. Yılmaz, S. Ülker and B. Kahveci, *Arch. Pharm. Chem. Life Sci.*, **2013**, *346*, 556-561.
25. B. Kahveci, F. Yılmaz, E. Menteşe and N. Karaali, *Letters in Organic Chemistry*, **2013**, *10*, 490-495.
26. A. Pinner "Die imidoether und ihre derivative", 1. Auflage, Oppenheim, Berlin, 1982.