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MICROWAE-ASSISTED ONE-POT THREE COMPONENT SYNTHESIS OF SOME NEW 4(3*H*)-QUINAZOLINONE DERIVATIVES

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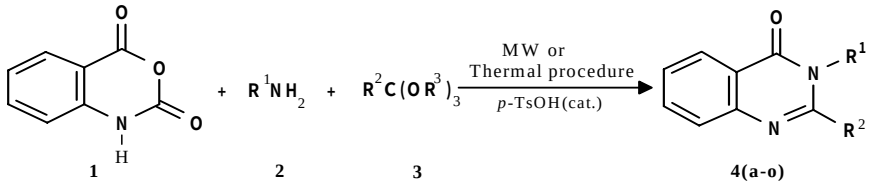
Abstract- Efficient microwave-assisted synthesis of 4(3*H*)-quinazolinones by the one-pot three-component condensation of isatoic anhydride, primary amines and orthoesters in the presence of catalytic amounts of *p*-toluenesulfonic acid in high yields is reported.

4(3*H*)-Quinazolinone is a frequently encountered heterocycle in medicinal chemistry with wide applications including antidiabetic,[1] antiinflammatory,[2] antibacterial,[3] anticonvulsant,[4] antihistaminic[5] and antitumor agents.[6] Thus, synthesis of this heterocyclic nucleus is a current importance. The most simple and straightforward procedure reported by Niementowski in 1895 includes 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]

Microwave irradiation has been extensively used for the rapid synthesis of a variety of heterocyclic compounds.[13] In this paper we wish to report a rapid, efficient and one-pot synthesis of 4(3*H*)-quinazolinones derivatives by a three-component reaction under microwave irradiation.

We have found that the condensation of isatoic anhydride **(1)** with primary amines **(2)** and orthoesters **(3)** in the presence of catalytic amounts of *p*-toluenesulfonic acid results in rapid formation of the corresponding 2,3-disubstituted 4(3*H*)-quinazolinones **(4a-o)** in a microwave oven and classical heating.(Scheme 1).

In all cases, the yields were optimized by power and time as indicated in Table 1. The results are summarized in Table 1.



1 2 3 4(a-o)

Scheme 1

Table 1: Synthesis of 2,3-Disubstituted Quinazolinones

Entry	Product	R^1	R^2	R^3	Lit.Yied (%)	Thermal[a] Procedure yield (%)	Yield[a,b]MW (%)	mp (°C)	Lit. mp (°C)
1	**4a**	*p*-ClC_6H_4	Me	Et	80[14]	69	76	159-160	157-158[14]
2	**4b**	*p*-MeC_6H_4	Me	Et	40[17]	78	83	150-152	148-150[17]
3	**4c**	Ph	Me	Et	38[17]	70	74	144-145	145-146[17]
4	**4d**	Ph	Ph	Me	90[16]	72	80	155-156	157[16]
5	**4e**	*p*-MeC_6H_4	Ph	Me	61[20]	75	91	179-181	180-181[19]
6	**4f**	*p*-BrC_6H_4	Et	Et	-	75	78	171-172	170-172[18]
7	**4g**	*p*-MeC_6H_4	Et	Et	-	81	85	162-164	163-164[15]
8	**4h**	Et	Et	Et	35[17]	81	89	93-94	95-96[17]
9	**4i**	Et	Me	Et	22[17]	78	87	63-65	64-65[17]
10	**4j**	$PhCH_2$-	Me	Et	31[17]	65	68	231-232	230-232[17]
11	**4k**	$PhCH_2CH_2$-	Me	Et	-	80	95	100-101	-
12	**4l**	$PhCH_2CH_2$-	Et	Et	-	76	92	103-104	-
13	**4m**	$PhCH_2CH_2$-	*n*-Pr	Me	-	81	92	105-106	-
14	**4n**	$PhCH_2CH_2$-	*n*-Bu	Me	-	82	96	109-110	-
15	**4o**	$PhCH_2CH_2$-	Ph	Me	-	78	93	175-176	-

[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] P/W 210, t/min 3 and [2] P/W 385, t/min 3).

Different kinds of substituted aromatic amines were subjected to the reaction with isatoic anhydride and a variety of orthoesters in the presence of catalytic amounts of *p*-toluenesulfonic acid, the products were isolated in good yields under microwave irradiation (irradiation conditions were [1] P/W 210, t/min 3 and [2] P/W 385, t/min 3) or thermal procedure in EtOH (Table 1, Entries 1-7). 2-Phenylethylamine, benzylamine and ethylamine as aliphatic model compounds were also reacted satisfactorily under the same conditions (Table 1, Entries 8-15).

The comparison of the yield percentage of those compounds reported previously,[14-20]showed that the yield in this work under microwave irradiation or thermal procedure is highly increased (Table 1).

In summary, we have described a facile and efficient procedure for the one-pot preparation of some novel 4(3*H*)-quinazolinones **(4k-4o)**. The method offers several advantages including high yield of products, short reaction times, cleaner reaction and easy experimental work-up procedure, which makes it a useful process for the synthesis of 4(3*H*)-quinazolinones.

EXPERIMENTAL

Products **(4a-4j)** are known compounds and their physical data, IR and ^{1}H NMR spectra and melting points were essentially identical with those of authentic samples. Products **(4k-o)** are new compounds and characterized by their spectroscopic data (IR, ^{1}H and ^{13}C NMR, MS spectra and elemental analysis).

Melting points were measured on the Electrothermal 9100 apparatus and are uncorrected. Infrared spectra were measured on a Shimadzu IR-470 Spectrophotometer. ^{1}H and ^{13}C NMR spectra were determined on a bruker 500 DRX AVNCE msiniment at 500 and 125 MHz, respectively. MS spectra were recorded on a Shimadzu QP 1100EX Mass Spectrometer operating at an ionization potential of 70 eV. CHN Elemental analyses were performed using a Heracus CHN-O-Rapid analyzer. Microwave irradiation were carried out in a National oven, model 5250, at 2450 MHz.

General Procedure Under Thermal Condition:

A mixture of isatoic anhydride **(1)** (1.034 g, 8.0 mmol), amine **(2)** (10 mmol), orthoester **(3)** (2 mL) and *p*-toluenesulfonic acid (5 mol%) was refluxed in EtOH for 5 h. In all cases, the yields were optimized by interrupting the reactions in each hour's period and monitoring the progress of the reaction by TLC. The reaction mixture was allowed to cool to rt and poured into water (150 mL). The precipitates were filtered and washed with water. Recrystalization from 96% ethanol gave 2,3-disubstituted 4 (3*H*)-quinazolinones **(4a-4o)** in good yield.

General Procedure under Microwave Irradiation:

Isatoic anhydride **(1)** (1.034 g, 8.0 mmol), amine **(2)** (10 mmol), orthoester **(3)** (2 mL) and *p*-toluenesulfonic acid (5 mol%) were mixed thoroughly in a tall beaker and covered with a stemless funnel which then placed in the microwave oven. The mixture was irradiated for two subsequent 3 min periods (irradiation conditions were [1] P/W 210, t/min 3, [2] P/W 385, t/min 3). In all cases, the yields were optimized by interrupting the reactions in each 1 min period and monitoring the progress of the reaction by TLC. The reaction mixture was allowed to cool to rt and the resultant residue poured in cool water (15 mL). The precipitated compound was filtered and washed with water. The crude solid product was recrystallized from EtOH to give the pure products **(4a-4o)** in good yield.

Spectral data for products (4k-4o):

2-Methyl-3-phenylethyl-4(3*H*)-quinazolinone (4k): white powder crystal, mp 100-101 °C. IR (KBr), (ν_{max} /cm^{-1}): 1680 (C=O). ^{1}H NMR ($CDCl_3$) δ: 2.90 (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: 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(3*H*)-quinazolinone (4l): white solid cotton form, mp 103-104°C. IR (KBr), (ν_{max} /cm^{-1}): 1680 (C=O). ^{1}H NMR ($CDCl_3$) δ: 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: 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(3*H*)-quinazolinone (4m): white crystal, mp 105-106 °C. IR (KBr), (ν_{max} /cm^{-1}): 1670 (C=O). ^{1}H NMR ($CDCl_3$) δ: 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: 13.95, 20.66, 34.92, 36.87, 45.57, 120.52, 126.28, 126.63, 126.89, 126.98, 128.83, 134.07, 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(3*H*)-quinazolione (4n): white crystal, mp 109-110 °C. IR (KBr), (ν_{max} /cm^{-1}): 1680 (C=O). ^{1}H NMR ($CDCl_3$) δ: 1.45 (t, *J*=7.37, 3H, CH_3), 1.91 (m, 2H, CH_2), 2.50 (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: 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(3*H*)-quinazolinone (4o): white powder needle forms, mp 175-176 °C. IR (KBr), (ν_{max} /cm^{-1}): 1667 (C=O). ^{1}H NMR ($CDCl_3$) δ: 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: 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.

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REFERENCES

1. M. S. Malamas and J. Millen, *J. Med. Chem*., 1991, **34**, 1492.
2. W. Nawrocka and J. J. Stasko, *Boll. Chim. Farm.*, 1998, **137**, 35.
3. S. D. Sharma and V. Kaur, *Synthesis*, 1989, 677.
4. A. Mannschreck, H. Koller, G. Stuhler, M. A. Davies, and J. Traber, *Eur. J. Med. Chem.*, 1984, **19**, 381.
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.
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. (a) F-R. Alexandre, A. Berecibar, R. Wrigglesworth, and T. Besson, *Tetrahedron*, 2003, **59**, 1413. (b) J. S. Yadav and B. V. S. Reddy, *Tetrahedron Lett.*, 2002, **43**, 1905. (c) H. Hazarkhani and B. Karimi, *Tetrahedron*, 2003, **59**, 4757.
13. For a review see: (a) P. Lidström, J. Tierney, B. Wathey, and J. Westman, *Tetrahedron*, 2001, **57**, 9225. (b) A. Loupy, A. Petit, J. Hamelin, F. Texier-Boullet, P. Jacquault, and D. Mathe, *Synthesis*, 1998, 1213. (c) M. S. Khajavi and A. A. Mohammadi, *J. Chem. Res. (s)*, 2002, 136. (d) J. Azizian, A. A Mohammadi, and A. R. Karimi, *Synth. Commun*., 2003, **33**, 415. (e) J. Azizian, A. A. Mohammadi, F. Ardakani, A. R. Karimi, and M. R. Mohammadizadeh, *Heterocycles*, 2004, **63**, 791.
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.
16. G. Rabilloud and B. Sillion, *J. Heterocycl. 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.