Catalyst and Solvent Free, Microwave Assisted Synthesis of 3-Isoindolo-2-yl-2-Substituted Quinazolin-4(3*H*)-Ones

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(Received on 23rd December 2011, accepted in revised form 4th May 2013)

Summary: In the present work, we document a new microwave asisted and direct thermal fussion method for preperation of 3-isoindolo-2-substituted-quinazolin-4(3*H*)-ones under solvent and catalyst free conditions. Both methods are much convineant, green and faster and high yielding. Microwave method was proved to be high yielding and faster as compared to the direct thermal fusion method.

Key words: 3-isoindolo-2-substituted quinazolin-4(3*H*)-ones; catalyst free, solvent free; direct thermal fusion; microwave assisted; synthesis.

Introduction

Quinazolin-4(3*H*)-one based heterocyclic compounds both natural and synthetic, show wide range of biological applications such as; anti-inflamatory, anticancer, cardiovascular activities, antihistamintic, antifungal, antiviral, antimalarial, hypothermic, psychotropic, hypnotic, CNS depressant, CNS stimulant, tranquilizing, antidepressant and anticonvulsant effects. Quinazolin-4(3*H*)-one scaffold is reported as an active structure in many drugs and is very important medicinal agent. This is found as dominant nucleus in a number of organic medicinal agents [1-13]. Because of their broad spectrum biological activities, they are long being known as a class of nitrogen containing heterocyclic compounds and have remained of considerable focus for organic and medicinal chemists. Consequently, sufficient literature is available describing the chemistry of quinazolin-4(3*H*)-ones [14, 15]. Since the past few decades synthetic chemists are more interested in the development of green, faster and cost effective synthetic methods both for new and reported organic compounds. Among these, the microwave assisted and solvent and catalyst free methods are of more interest for the researchers [16]. Quinazolin-4(3*H*)-one ring skeleton and quinazolin-4(3*H*)-one based compounds have been synthesised using microwave techniques [16]. We herein have made a successful attempt of synthesizing 3-heteroaryl-quinazolin-4(3*H*)-ones using microwave irradiation in good yield without using any catalyst and solvent. The newly established method has also been compared with direct thermal fusion method.

Results and Discussion

3-Heteroaryl-quinazolin-4(3*H*)-ones are important class of quinazolinones based alkaloids and potent antimicrobial agents. Literature describes preparation of 3-alkyl/aryl-quinazolin-4(3*H*)-ones and related compounds via condensation of 3-aminoquinazolin-4(3*H*)-ones and other oxo-cyclic compounds in glacial acetic acid and chloroform under reflux [16, 17]. The resultant products however, are of low yield; *i.e*., 22% [16] and 30-50% [17]. The developed methods also require tedious reaction workup and the formation of side products. Our on-going research on chemistry of quinazolin-4(3*H*)-ones has resulted in several new bioactive quinazolin-4(3*H*)-ones and also new methods for the synthesis the same and its derivatives [18-21]. Here in we report the development of two new methods, *i.e*., synthesis via microwave assisted and direct thermal fusion at high temperature (Scheme-1). In the first method, we synthesized 3-isoindolo-2-yl-2-substituted quinazolinones (**1-3**) by irradiating the mixture of 2-alkyl-3-aminoquinazolin-4(3*H*)-ones and phthalic anhydride for 8-13 min in a domestic microwave oven at interval of consecutive pulses for 30-60 seconds. After completion of reaction, the products were recrystallized from ethanol.

In second method, phthalic anhydride and 2-aryl/alkyl-3-aminoquinazolin-4(3*H*)-ones, mixed to gather fused at 150 ^{0}C for 30 min., upon completion as shown by using TLC, the molten contents were cooled and the solid products appeared upon cooling were then recrystallized from ethanol. Both the methods were found to be high yielding and faster as compared to the already reported methods in the solution phase [16, 17]. While comparing the newly developed methods, microwave assisted method was found even more convenient, faster with much high yielding as compared to direct thermal fusion method (Table-1). In conclusion, both the methods are

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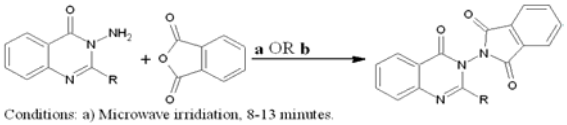
convenient and can be easily used for the synthesis of 3-heteroaryl-quinazolinones and their other analogues.

Structural investigation was done using advanced spectroscopic techniques including; ^{1}H-NMR (Bruker, 300 MHZ), FT-IR and Mass (MAT-312, Jeol) spectrometry of all compounds synthesized. All the compounds showed characteristics molecular ion peaks at *m/z* 291, 305 and 367 for compounds 1, 2 and 3 respectively and showed characteristics fragmentation pattern as well. All the compounds showed peaks at *m/z* 146, providing evidence for the formation of 1*H*-isoindole-1,3(2*H*)-dione part in all the three molecules during fragmentation. ^{1}H-NMR spectrum gave a down field singlet at 10.23 ppm indicating single hydrogen at position **2** of the quinazolin-4(3*H*)-one part of molecule, similarly ^{1}H-NMR spectrum of compound **2** *i.e*. 3-(1,3-dihydro-2*H*-isoindol-2-yl)-2-methyl-quinazolin-4(3*H*)-one showed a singlet at 2.48 ppm showing methyl side chain at position **2** of quinazolin-4(3*H*)-one part, while ^{1}H-NMR spectrum of all the three compounds showed typical absorption peaks for aromatic proton. Thus, ^{1}H-NMR spectrum of compound **1** showed a doublet at 8.29, singlet at 8.01, triplet at 7.89, triplet at 7.78, triplet at 7.6 and triplet at 7.55-7.51 ppm, respectivally for aroamtic protons. ^{1}H-NMR spectrum of compound **2** showed doublet at 8.21, doublet of doublet at 8.019-7.99, doublet at 7.89, triplet at 7.82-7.767, doublet at 7.717 and triplet 7.5-7.45, while ^{1}H-NMR spectrum of compound **3** showed doublet at 8.24, doublet at 8.21, doublet of doublet at 7.99, triplet at 7.85, doublet at 7.73, triplet at 7.67, multiplet at 7.62, triplet at 7.59 and triplet at 7.56 ppm for aromatic protons.

Mechanistically, the reaction is believed to take place via the initial opening of phthalic anhydride and formation of an amide intermediate via nucleophilic attack of $-NH_2$. The amide intermediate then cyclize via internal nucleophilic attack by nitrogen is followed by elimination of water to give the target 3-isoindolo-2-yl-2-substituted quinazolin-4(3*H*)-one (1-3) in substantial yield (Table-1)



Scheme-1: Synthesis 2-(2-alkyl/aryl-4-oxoquinazolin-3(4H)-yl-1-*H*-isoindol-1,3 (2H)-dione (**1-3**).

Table-1: Comparative reaction time and yield of 2-(2-alkyl/aryl-4-oxoquinazolin-3(4*H*)-yl) 1*H*-isoindole-1, 3(2*H*)-diones synthesized via method A and B **(1-3).**

Entry	R	Method	Time (Minutes)	Yield (%)
1	H	A	12	91
		B	30	83
2	CH_3	A	8	99
		B	30	85
3	Phenyl	A	13	97
		B	30	91

Method A: Microwave irradiation, 8-13 minutes; Method B: direct thermal fusion at high temperature.

Experimental

*Method A: Microwave Assisted Synthesis (**1-3**)*

3-(1,3-dihydro-2H-isoindol-2-yl)quinazolin-4(3H)-one **(1)**

Mixture of 3-aminoquinazolin-4(3*H*)-one (0.01g, 0.062 mmol.) and 2-benzofuran-1, 3-dione (0.01 g, 0.062 mmol.) were irradiated for 12 min in domestic microwave oven providing consecutive pulses for 30-60 sec. Upon completion, the reaction mixture was washed with water followed recrystallization with ethanol or chromatographed silica column using ethylacetate/hexane (1:9) to collect the product in pure form. Yield: 93%; m.p.: 176-180 ºC; EI-MS m/z: 291 (M^+, 8), 290 (25), 265 (10), 160 (21), 146 (51), 145 (100), 132 (45), 121 (12), ^{1}H-NMR (300 MHz) δ (ppm): 10.23 (s, 1H), 8.29 (d, 1H, *J*=7.57), 8.01(1, 2H, *J*=8.73), 7.89 (t, 1H, 8.2), 7.78 (t, 1H, 7.7), 7.6 (t, 2H, *J*=8.56), 7.55-7.51(t, 1H, *J*=8.23)

3-(1,3-Dihydro-2H-isoindol-2-yl)-2-methylquinazolin-4(3H)-one **(2)**

3-Amino-2-methylquinazolin-4(3*H*)-one (0.01 g, 0.05714 mmol.), 2-benzofuran-1, 3-dione (0.0845 g, 0.05714 mmol.) mixed to gather were subjected to microwave irradiation for 8 min providing consecutive pulses for 30-60 seconds. After completion of the reaction, crude product was recrystallized from water-ethanol mixture.

Yield: 91%; m.p.: 167-169 ºC; EI-MS m/z: 305 (M^+, 9), 26 2 (2), 166 (3), 146 (22), 123 (6), 122 (87), 105 (100), 104 (35), 92 (17), 77 (49), 76 (63), 65 (46), 51(36); ^{1}H-NMR(δ ppm): 8.21 (d, 1H, *J*=7.83), 8.0196-7.99 (dd, 2H, *J*=8.57), 7.89 (d, 2H, *J*=8.565), 7.822-7.767 (t, 1H, *J*=8.2), 7.717 (d, 1H, *J*=7.7), 7.5-7.452 (t, 1H, *J*=7.3), 2.48 (s, 3H, CH_3)

3-(1,3-Dihydro-2H-isoindol-2-yl)-2-phenylquinazolin-4(3H)-one **(3)**

3-Amino-2-phenylquinazolin-4(3*H*)-one (0.2 g, 0.843 mmol.) and 2-benzofuran-1, 3-dione (0.1248 g, 0.843 mmol.) in an open mouth Vaile was subjected to microwave irradiation for 13 min. The

resulting product formed was purified by recrystallization with dilute ethanol. Yield: 99%; m.p.: 68-69 ^{o}C; EI-MS m/z: 367 (M^{+}, 13), 290 (37), 222 (57), 208 (73), 180 (14), 146 (89), 133 (11), 105 (100), 92 (48), 65 (12), 51 (13): ^{1}H-NMR (δ ppm); 8.24 (d, 1H, *J*=8.2), 8.21 (d, 2H, *J*=7.8), 7.99 (dd, 2H, *J*=8.67), 7.85 (t, 1H, *J*=8.56), 7.73 (d, 1H, 8.2), 7.67 (t,1H, *J*=8.7), 7.62 (m, 2H), 7.59 (t, 2H, *J*=8), 7.56 (t, 1H, *J*=8.6).

Method B: Synthesis via Thermal Fusion
Typical Synthesis of 3-(1,3-dihydro-2H-isoindol-2-yl)quinazolin-4(3H)-one **(1)**

2-methyl-3-aminoquinazolin-4(3*H*)-one (0.05 g, 0.28 mmol.), 2-benzofuran-1, 3-dione (phthalic anhydride) (0.042 g, 0.28 mmol.) mixed to gather were thermally fused for 30 min at 150 ^{o}C. The reaction contents upon cooling resulted in crude solid product. The crude product after recrystallization with water-ethanol mixture resulted in pure product. (Yield; 83%; m. p. 176-178 ^{o}C)

Acknowledgemnets

The authors are thankful to HEJ-RIC, University of Karachi, Pakistan for providing access to spectroscopic facilities.

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