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ECOFRIENDLY SYNTHESIS OF 4-(3*H*)-QUINAZOLINONES BY MICROWAVE ASSISTED TANDEM REACTION.

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ABSTRACT

A one pot synthesis of quinazolinone derivatives from the reaction of anthranilic acid and primary aromatic amines with Vilsmeier reagent (DMF/$POCl_3$) has been carried out. The methodology is environmentally benign and completely eliminates the need of solvent for the reaction. Neat reactants were cyclocondensed under microwaves to afford the reaction occurred in a few minutes using microwave assisted providing excellent yields. Their structures have been elucidated on the basis of elemental analyses and spectroscopic studies (IR, ^{1}H-NMR, MS)

KEYWORDS

Synthesis, Quinazolinone derivatives, Vilsmeier reagent, microwave assisted

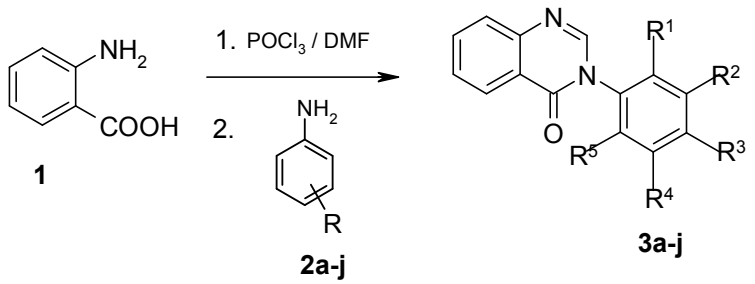
INTRODUCTION

4-(3*H*)-Quinazolinones are important class of fused heterocycles with a wide range of biological activities such as anti-cancer,[1] anti-inflammatory,[2] anticonvulsant,[3] antihypertensive,[4] antimalarial[5] and anti-HIV.[6] Similarly, quinazoline containing moieties have been known as tyrosine kinase inhibitors[7], dihydrofolate reductase inhibitors[8] and tubulin polymerization inhibitors.[9] Conventional methods for the preparation of Quinazolinones involve cycloaddition of anthranilic acid derivatives with a diverse range of substrates including imidates and iminohalides.[10] Salehi *et al* synthesized quinazolin-4-(*3H)*one derivatives *via* one pot three component reaction of isatoic anhydride and an orthoester with ammonium acetate or a primary amine catalyzed by silica-sulfuric acid under solvent free conditions.[11] Dai *al et* achieved the synthesis of 2-methyl-3-(2(diphenylphosphino)phenyl-4(3*H*)-Quinazolinones by coupling *N*-acetylanthranilic acid with the corresponding phosphinoanilines.[12] Liu *et al* have developed a microwave assisted, one pot-two step synthesis of Quinazolinones from anthranilic acids, carboxylic acids or acyl chlorides and amines.[13] Abdel-jalil *et al* have reported that the condensation of anthranilamide with alkyl, aryl or heteroaryl aldehydes in refluxing ethanol and t $CuCl_2$ afforded the corresponding 2-substituted Quinazolinones in excellent yields.[14] Deetz *et al* studied the cyclocondensation of 2-fluoro substituted benzoyl chlorides with 2-amino-*N*-heterocycles to form 4(3H)-Quinazolinones. [15] Hazarkhani *et al* described the preparation of 2-amino-N-(1-H-benzimidazol-22-yl)benzamide and a variety of new 3-(2- benzimidazolyl)-2-alkyl-4-(3H)-Quinazolinones using isatoic anhydride2-aminobenzimidazole and orthoesters under microwave irradiation.[16] Kamal *et al* studied the conversion of 2-azido/2-nitro benzoic acids to 4(3*H*)-Quinazolinones under microwave irradiation.[17] Wang *et al* reported an efficient synthesis of Quinazolinones from anthranilic acid, ortho esters and amines using $Yb(OTf)_3$ in one-pot under solvent-free condition at 80°C.[18] Narasimhulu *et al* reported the one-pot synthesis of Quinazolinones derivatives from the reaction of anthranilic acid trialkyl orthoformate and amines in the presence of lanthanum(III)nitrate hexahydrate or p-toulenesulfonicacid.[19] Khosropour *et al* synthesized 4(3H)Quinazolinones in high to excellent yields through the one –pot condensation of anthranilic acid trimethyl orthoformate and primary amines in the presence of 5 mol % of $Bi(TFA)_3$ immobilized on $\{nbp\}FeCl_4$ as a room temperature ionic liquid.[20] However, some of these methods are associated with drawbacks such as multistep procedures, costly reagents, harsh reaction conditions, long reaction time, complex and tedious experimental procedures and low yields. Thus the development of new and simple methodologies for these heterocycles is highly desirable. As part of our ongoing interest in developing new methods for the synthesis of various heterocyclic scaffolds[21], we herein disclose an efficient method for the synthesis of 4-(3H)-Quinazolinones through the reaction of anthranilic acid and primary aromatic amines

under Vilsmeier conditions (DMF/$POCl_3$) under microwave irradiation method (**Scheme1**).

RESULTS AND DISCUSSION

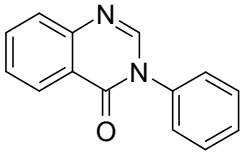
Anthranilic acid was treated with Vilsmeier reagent at 0 ^oC and the reaction mixture was stirred until TLC monitoring indicated the disappearance of anthranilic acid. Subsequently aniline was added to the reaction mixture and supported on sodium suphate and subjected to microwave irradiation. The reaction was quenched with water and extracted with ethyl acetate, dried over sodium sulphate, concentrated and column purified. IR absorption at 1668 and 1591 cm^{-1} corresponding to carbonyl and imine functionality respectively indicated the formation of the product. Further a singlet at 8.11 ppm for quinazolinone proton confirmed the formation of the product. Following the same procedure substituted anilines were treated with anthranilic acid and Vilsmeier reagent under microwave conditions (**Scheme 1)** and the results are summarized in **Table 1.**

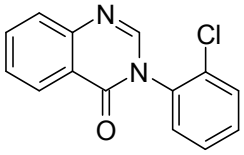
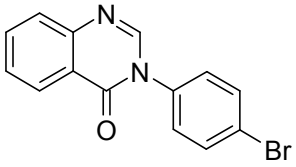
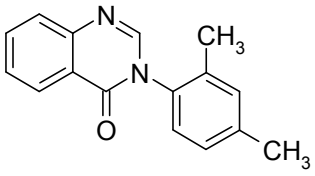
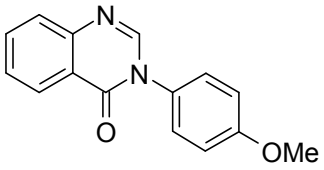
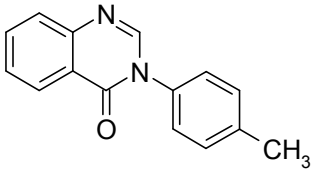
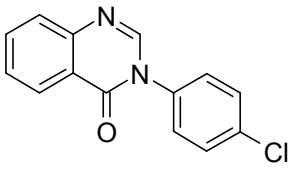
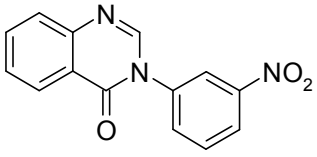


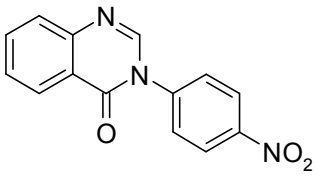
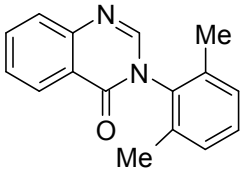
Scheme 1

Various 4(3H)-Quinazolinones **3a**-**3j** were synthesized (**Table 1**) by treating anthranilic acid **1** with Vilsmeier reagent (DMF/$POCl_3$) at 0° C followed by the addition of primary aromatic amines(**3a-j**). The reaction mixture was supported onto anhydrous sodium sulphate and exposed to microwave irradiation for 2-4 minutes, resulting in the formation of 3-substituted Quinazolinones. The products were characterized by IR, NMR and Mass spectra.

Table 1
Synthesis of 3-substituted Quinazolinones

Entry	Quinazolinone	Reaction time (Min)	Yield (%)	M.P (°C)
1.	 **3a**	1.5	83	132

2.	 **3b**	1.7	81	178
3.	 **3c**	1.5	88	200
4.	 **3d**	1.7	84	Liquid
5.	 **3e**	2	85	240
6.	 **3f**	2	83	152
7.	 **3g**	1.9	84	194
8.	 **3h**	2	84	200

9.	 **3i**	2	85	198
10.	 **3j**	2	84	Liquid

Summary:

We have developed an efficient microwave-assisted, one-pot, tandem, two-step synthesis of 3-substituted Quinazolinones from anthranilic acid, Vilsmeier reagent and various primary aromatic amines. These results demonstrate the value of microwave-assisted chemistry in providing increased yields in shortened reaction times, in addition to expand the accessible chemical space by generating otherwise unavailable reaction products.

Experimental section :

General procedure for the synthesis of 4-(3H)-Quinazolinones: To an ice-cold solution of $POCl_3$ in DMF was added anthranilic acid (0.01458 mol) and stirred for 5-10 minutes until TLC indicated the disappearance of anthranilic acid. The reaction mixture was treated with the respective primary aromatic amine (0.01458 mol) and supported on to anhydrous sodium sulphate (five times the weight of anthranilic acid) and exposed to micro wave (BPL company) irradiation (600 Watts) for 2-4 minutes with 30sec pulse. The reaction mixture was quenched with water (50 mL) and extracted with ethyl acetate (2 x50mL). The organic layer was dried over anhydrous sodium sulphate, concentrated and purified by silica gel column chromatography (60-120 mesh) using hexane/EtOAc (7.5:2.5) as eluent to yield the pure product.

3-Phenyl-4-(3*H*)quinazolinone 3a : Brown crystals ,^{1}H NMR ($CDCl_3$, 500MHz, ppm): δ 7.41 (d, *J* = 6.9 Hz, 2H), 7.46 (t, *J* = 7.65 Hz, 1H), 7.52 (t, *J* = 6.9 Hz, 3H), 7.74 (t, *J* = 7.65 Hz, 1H), 7.79 (d, *J* = 8.4 Hz, 1H), 8.11 (s, 1H), 8.35 (d, *J* = 7.6 Hz, 1H). IR (KBr): 3057, 1668, 1591, 1464 cm^{-1}. MS (m/z) : 223 (M^++1). Anal Cacd for $C_{14}H_{10}N_2O$: C, 75.66; H, 4.54; N, 12.60. Found : C, 75.57; H, 4.56; N, 12.58.

3-(2-Chlorophenyl)-4-(3 *H*)quinazolinone 3b : Yellowcrystals, ^{1}H NMR ($CDCl_3$, 500MHz, ppm): δ 7.43-7.47 (m, 3H), 7.53 (t, *J* = 6.9 Hz, 1H), 7.59 (d, *J* = 6.9 Hz, 1H), 7.77 (d, *J* = 8.4 Hz, 1H), 7.79 (t, *J* = 8.4 Hz, 1H), 7.94 (s, 1H), 8.35 (d, *J* = 7.65 Hz, 1H). IR (KBr): 3061, 1677, 1603, 1082 cm^{-1}. MS (m/z): 257(M^++1), 259 (M^++3). Anal Cacd for $C_{14}H_9ClN_2O$: C, 65.51; H, 3.53; N, 10.91. Found : C, 65.60; H, 3.56; N, 10.89.

3-(4-Bromophenyl)-4-(3 *H*)quinazolinone 3c : yellowish brown crystal, ^{1}H NMR ($CDCl_3$, 500MHz, ppm): δ 7.29 ((d, *J* = 9.2 Hz, 2H), 7.52 (t, *J* = 6.9 Hz, 1H), 7.65 (d, *J* = 8.4 Hz, 2H), 7.73 (d, *J* = 8.4 Hz, 1H), 7.77 (t, *J* = 6.9 Hz, 1H), 8.06(s, 1H), 8.32 (d, *J* = 8.4 Hz, 1H).

IR (KBr): 3094, 1696, 1604, 1070 cm^{-1}. MS (m/z) : 301 (M^++1), 303 (M^++3). Anal Cacd for $C_{14}H_9BrN_2O$: C, 55.84; H, 3.01; N, 9.30. Found : C, 55.92; H, 2.89; N, 9.31.

3-(2, 4-Dimethylphenyl)-4-(3*H*)quinazolinone 3d : Brown liquid,^{1}H NMR ($CDCl_3$, 500MHz, ppm): δ 2.14 (s, 3H), 2.38 (s, 3H), 7.10 (q, *J* = 7.65 Hz, 2H), 7.18 (s, 1H), 7.51 (t, *J* = 8.4 Hz, 1H), 7.75 (m, 2H), 7.97 (s, 1H), 8.34 (d, *J* = 8.4 Hz, 1H). IR (neat): 1922, 1685, 1605 cm^{-1}. MS (m/z) : 251 (M^++1). Anal Cacd for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.19. Found : C, 76.85; H, 5.63; N, 11.21.

3-(4-Methoxyphenyl)-4-(3 *H*)quinazolinone 3e : White crystals,^{1}H NMR ($CDCl_3$, 500MHz, ppm): δ 3.85 (s, 3H), 7.02 (d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 9.1 Hz, 2H), 7.51 (t, *J* = 6.9 Hz, 1H), 7.73 (d, *J* = 7.65 Hz, 1H), 7.77 (d, *J* = 8.4 Hz, 1H), 8.10 (s, 1H), 8.34 (d, *J* = 8.4Hz, 1H). IR (KBr): 3048, 2982, 1682, 1609, 1261, 1034 cm^{-1}. MS (m/z) : 253 (M^++1). Anal Cacd for $C_{15}H_{12}N_2O_2$: C, 71.42; H, 4.79; N, 11.10. Found : C, 7135; H, 4.81; N, 11.08.

3-(4-Methylphenyl)-4-(3*H*)quinazolinone 3f : Yellowishwhitecrystals,^{1}H NMR ($CDCl_3$, 500MHz, ppm): δ 2.42 (s, 3H), 7.28 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 8.4 Hz, 2H), 7.51 (t, *J* = 8.4 Hz, 1H), 7.73 (t, *J* = 7.65 Hz, 1H), 7.76 (d, *J* = 6.9 Hz, 1H), 8.10 (s, 1H), 8.34 (d, *J* = 6.9 Hz, 1H). IR (KBr): 3047, 1689, 1600 cm^{-1}. MS (m/z) : 237 (M^++1). Anal Cacd for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86. Found : C, 76.32; H, 5.10; N, 11.87.

3-(4-Chlorophenyl)-4-(3*H*)quinazolinone 3g :Yellowcrystals, ^{1}H NMR ($CDCl_3$, 500MHz, ppm): δ 7.35 (d, *J* = 9.2 Hz, 2H), 7.50 (d, *J* = 9.2 Hz, 2H), 7.54 (d, *J* = 6.9 Hz, 1H), 7.74 (d, *J* = 7.65 Hz, 1H), 7.78 (t, *J* = 8.4 Hz, 1H), 8.07 (s, 1H), 8.32 (d, *J* = 9.2 Hz, 1H). IR (KBr): 3053, 1696, 1604, 1095 cm^{-1}. MS (m/z) : 257 (M^++1), 259 (M^++3). Anal Cacd for $C_{14}H_9ClN_2O$: C, 65.51; H, 3.53; N, 10.91. Found : C, 65.60; H, 3.55; N, 10.92.

3-(3-Nitrophenyl)-4-(3*H*)quinazolinone 3h : Browncrystals, ^{1}H NMR ($CDCl_3$, 500MHz, ppm): δ 7.29 (d, *J* = 6.9 Hz, 1H), 7.32 (t, *J* = 6.9 Hz, 1H), 7.50 (d, *J* = 8.4 Hz, 1H), 7.55 (d, *J* = 7.45 Hz, 1H), 7.57 (t, *J* = 7.65 Hz, 1H), 7.59 (t, *J* = 8.4 Hz, 1H), 7.77 (d, *J* = 8.4 Hz, 1H), 8.01 (s, 1H), 8.11 (s, 1H). IR (KBr): 3059, 1699, 1540, 1350, 1611 cm^{-1}. MS (m/z) : 268 (M^++1). Anal Cacd for $C_{14}H_9N_3O_3$: C, 62.92; H, 3.39; N, 15.72. Found : C, 62.85; H, 3.38; N, 15.73.

3-(4-Nitrophenyl)-4-(3*H*)quinazolinone 3i : Browncrystals ,^{1}H NMR ($CDCl_3$, 500MHz, ppm): δ 7.29 (d, *J* = 6.9 Hz, 1H), 7.52 (t, *J* = 8.4 Hz, 1H), 7.65 (d, *J* = 8.4 Hz, 1H), 7.74 (d, *J* = 7.45 Hz, 2H), 7.77 (t, *J* = 6.9 Hz, 1H), 7.84 (d, *J* = 7.45 Hz, 2H), 7.89 (s, 1H). IR (KBr): 3055, 1666, 1545, 1348, 1608 cm^{-1}. MS (m/z) : 268 (M^++1). Anal Cacd for $C_{14}H_9N_3O_3$: C, 62.92; H, 3.39; N, 15.72.. Found : C, 62.99; H, 3.41; N, 15.70.

3-(2, 6-Dimethylphenyl)-4-(3*H*)quinazolinone 3j : Brownliquid,^{1}H NMR ($CDCl_3$, 500MHz, ppm): δ 2.06, (s, 6H), 7.11 (d, *J* = 7.65 Hz, 2H), 7.18 (t, *J* = 8.4 Hz, 1H), 7.43 (t, *J* = 6.9 Hz, 1H), 7.69 (t, *J* = 8.4 Hz, 1H), 7.73 (d, *J* = 6.9 Hz, 1H), 7.82 (s, 1H), 8.32 (d, *J* = 9.2 Hz, 1H). IR (KBr): 3045, 1688, 1610 cm^{-1}. MS (m/z): 251 (M^++1). Anal Cacd for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.19. Found : C, 76.85; H, 5. 67; N, 11.20.

REFERENCES

1. Wolfe J F, Rathman T L, Sleevi M C, Campbell J S A & Greenwood T D, *J. Med. Chem*. 33, 1990, 161.
2. Tereshima K, Shimamura H, Kawase A, Tanaka Y, Tanimura T, Kamisaki T, Ishizuka Y & Sato *M*, *Chem.Pharm. Bull*.45,1995, 2021.
3. Kurogi Y, Inoue Y, Tsutsumi K, Nakamura S, Nagao K ,Yohsitsug H & Tsuda Y, *J . Med. Chem*.39, 1996, 1443.
4. Liverton N J, Armstong D J, Claremon D A, Remy D C, Baldwin J J, Lynch R J ,Zhang G & Gould R, *Bioorg. Med. Chem. Lett*. 39, 1998, 483.
5. Gueyrard D, Gurnel V, Leoni O, Palmieri S & Rollin P, *Heterocycles* 32,2000, 827.
6. Pandeya S N, Sriram D , Nath G & Declerca E *Pharmaceutica Acta Helvetiae* 74, 1999, 11
7. Rewcastle G W, Denny W A, Bridges A J, Zhou H, CodR & McMichael A, Fry D W,*J.Med.Chem*.38,1995,3482.
8. Rosowsky A, Mota, C E,Wright J E & Queener S F, *J.Med.Chem*.37, 1994, 4522.
9. Jiang J B, Hesson D P, Dusak B A, Dexter D L, Kang G L & Hamel E, *J Med.Chem*. 33, 1990, 1721.
10. Majo V J & Perumal P T, *Tetrahedron lett*, 37,1996, 5015.
11. Salehi P, Dabiri M, Zolfigol M A & Baghbanzadeh M, *Tetrahedron Lett*.46,2005,7051.
12. Dai X,Wong A & Virgil S C, *J Org.chem* 63,1998,2597
13. Liu J F, Lee J, Dalton A M, Grace Bi G,Yu L, Baldino C M, McElory E & Brown M,*TetrahedronLett*,46,2005,1241
14. Abdel Jalil R J, Voelter W & Saeed M,*TetrahedronLett 45,*2004,3475.
15. Deetz M J, Malaerich J P, Beatty A M & Smith B D,*TetrahedronLett*.42,2001,1851.
16. Hazarkhani H& Karimi B, *Tetrahedron Lett* 59, 2003,4757.
17. Kamal A, Reddy K S,Prasad B R, HariBabu A & Ramana AV,*TetrahedronLett*.45,2004,6517.
18. Wang L, Xin J, Qin F& Qian C ,Sun J.*Synthesis* 2003,1241.
19. Narasimhulu M, Mahesh K C, Reddy T S, Rajesh K & VenkateswarluY,*Tetrehedron Lett*.47,2006,4381
20. Khosropour A R,MohammadpoorBaltorkal & Ghorbankhani H,*Tetrahedron Lett*.47, 2006, 3561.
21. (a) ZulykamaY, Perumal P T, *Aust. J. Chem*. 60, 2007, 205. (b) Praveen C,Sagayaraj Y&Perumal P T, *Tetrahedron Lett*. 50, 2009, 644. (c) Zulykama Y, Nagarajan,Perumal P T, *Syn. Comm*. 34,2004, 1309.