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A NEW EFFICIENT METHOD FOR THE THREE-COMPONENT SYNTHESIS OF 4(3*H*)-QUINAZOLINONES

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Abstract – 4(3*H*)-Quinazolinones were efficiently synthesised by the three component cyclisation-oxidation of isatoic anhydride, ammonium acetate and aromatic aldehydes in the presence of ceric ammonium nitrate in ethanol.

4(3*H*)-Quinazolinones are important class of bioactive molecules and widely used as anticonvulsant, anticancer, antimalarial, antihypertensive and antiinflammatory agents.[1] 4(3*H*)-Quinazolinone moiety is present in several bioactive natural products.[2,3] Among them 2-substituted 4(3*H*)-quinazolinones reported to possess a wide range of biological and pharmaceutical activities such as growth inhibitory against leukemia cells,[4] poly(ADP-ribose)polymerase,[5] and panel of tumor cell lines.[6] Some other derivatives of this family have been used in the study of potential anthelmintics,[7] antiallergic[8] and antitubercular agents.[9]

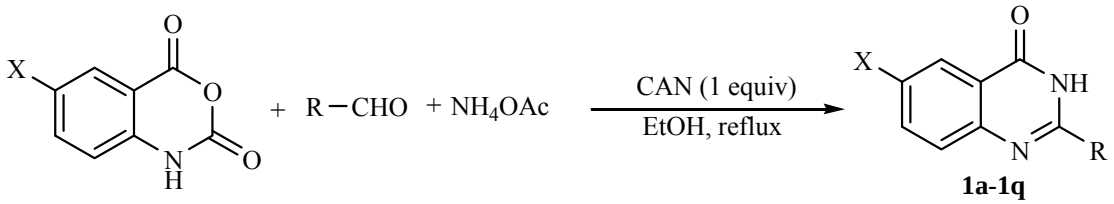
Due to the importance of 2-substituted quinazolinones different synthetic strategies for their synthesis have been described in the literature.[10] The most common approach involves amidation of 2-aminobenzonitrile, 2-aminobenzoic acid and 2-aminobenzamide[11] and some modification of this procedure that have also been reported.[12] Other methods such as reaction of anthranilic acid with substituted imidates,[13] aldehydes,[14] and reductive cylization of 2-nitrobenzamides were also reported.[15] However, some of these methods are associated with certain drawbacks such as a multi-step procedure,[13] costly reagents,[15] harsh reaction conditions,[16] complex experimental process, long reaction times,[11] and low yields.[11] Therefore, there is still a need to develop appropriate efficient and versatile methods for the synthesis of 4(3*H*)-quinazolinones.

Recently, multi-component condensation reactions have become a powerful method for the synthesis of small-molecule libraries, due to the fact that products are formed in a single step by simultaneous reactions of several reagents and the molecular diversity required for such combinatorial libraries can be achieved by simply varying each component.[17]

Ceric ammonium nitrate (CAN), was first investigated in 1936.[18] CAN has received considerable attention as an inexpensive and easily available catalyst for various organic reactions such as oxidation, oxidative addition, nitration, photo-oxidation, deprotection, graft polymerization, etc.[19]

In continuation of our interest in finding convenient methods for the synthesis of quinazolinone derivatives,[20] we wish to report a novel and effective method for the synthesis of these class of compounds.

When CAN was added to a mixture of isatoic anhydride, ammonium acetate and aldehyde in ethanol under reflux condition the desired products (**1a-1q**) were afforded after an appropriate time (Scheme 1).



Scheme 1

The results are summarised in Table 1. The reaction of different aromatic and aliphatic aldehydes and two derivatives of isatoic anhydride were conducted in ethanol and in all cases the desired products were obtained successfully. Another advantage of this method is the use of easily available aldehydes for the installation of C_2 substituents. Therefore, a wide range of 2-substituted 4(3*H*)-quinazolinones could be synthesized by a one-pot three-component reaction that is very important in view of combinatorial chemistry in drug discovery. It is worthy to note that there are some reports on the application of aldehydes in the synthesis of 4(3*H*)-quinazolinones, but they took place through two or three step reaction.[14] Aliphatic aldehydes work well under reaction condition and afforded the corresponding products in good yields (Table 1, Product **1l** and **1m**). Furthermore, the heterocyclic aldehydes such as furfural also worked well without the formation of any side products (Table 1, product **1k**). Work up procedure was so simple including isolation of products by simple aqueous work-up followed by filtration.

In conclusion a novel one-pot procedure for the synthesis of 2-substituted 4(3*H*)-quinazolinones was introduced. The reaction has been shown to display good functional group tolerance and is high yielding and the product isolation is very straightforward. We hope that this approach may be of value to others seeking novel synthetic fragments with unique properties for medicinal chemistry programs.

Table 1. Synthesis of 2-substituted 4(3*H*)-quinazolinones (**1**)

Product	X	R	Time(h)	Yield(%)[a]	Mp (°C)	
					Found	Reported[b]
1a	H	C_6H_5	3	85	233-234	235[12f]
1b	H	2-HO-C_6H_4	3.5	75	250 (dec.)	-
1c	H	3-O_2N-C_6H_4	4	78	>300	>300[14f]
1d	H	4-O_2N-C_6H_4	5	75	>300	>300[14f]
1e	H	4-MeO-C_6H_4	3.5	80	246-247	245-246[14g]
1f	H	2,4-$(MeO)_2$-C_6H_3	4	79	206-207	206-207[14g]
1g	H	3,4-$(MeO)_2$-C_6H_3	3	83	220-222	-
1h	H	4-Cl-C_6H_4	3.5	82	>300	304[12f]
1i	H	2,4-$(Cl)_2$-C_6H_3	5	75	250 (dec.)	-
1j	H	4-Me-C_6H_4	3	86	240-242	241[12f]
1k	H	2-Furyl	4	73	220-222	221-222[14c]
1l	H	Me	7	60	235-236	238-239[20a]
1m	H	*n*-Pr	9	55	205-206	206-207[20a]
1n	Cl	C_6H_5	2.5	86	208-209	210[12f]
1o	Cl	2-Cl-C_6H_4	4	83	219-221	222[12f]
1p	Cl	4-Cl-C_6H_4	3	87	>300	303[12f]
1q	Cl	2-Me-C_6H_4	3	83	267-269	268[12f]

[a]Isolated yield based on isatoic anhydride.

[b]The products were characterised by comparison of their spectroscopic and physical data with authentic samples synthesised by reported procedures.

EXPERIMENTAL

Melting points were obtained in open capillary tubes and also were measured on the electrothermal 9100 apparatus and are uncorrected. Mass spectra were recorded on a Shimadzu QP 1100 BX Mass Spectrometer.

CHN Elemental analysis was performed using a Heracus CHN-O-Rapid analyser. IR spectra were recorded on KBr pellets on a Shimadzu IR-470 Spectrophotometer. ^1H and ^{13}C NMR spectra were determined on a Bruker 300 DRX AVANCE instrument at 300 and 75 MHz, respectively.

General procedure for the synthesis of 2-substituted 4(3*H*)-quinazolinones

Isatoic anhydride (1 mmol), ammonium acetate (1.2 mmol, 0.1 g), aldehyde (1 mmol) and EtOH (5 mL) were mixed in a round bottom flask. CAN (1 mmol, 0.548 g) was added and the mixture was stirred at 70

˚C under reflux condition for the appropriate time (see Table 1). After completion of the reaction was confirmed by TLC (eluent: EtOAc/*n*-hexane: 1/2), the solvent was evaporated. Water was added and the precipitated product was filtered. Finally, the crude quinazolinone was recrystallised from EtOH.

2-(2-Hydroxyphenyl)quinazolin-4(3*H*)-one (1b). Pale yellow powder, mp 250 ℃ (decomp.). IR (KBr) υ/cm: 3440, 3098, 1673, 1610, 1563, 1506, 1397, 1333. ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 6.93-7.01 (m, 2H, Ar-H), 7.42-7.56 (m, 2H, Ar-H), 7.70-8.23 (m, 4H, Ar-H), 12.47 (s, 1H, NH), 13.79 (s, 1H, OH). ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm): 114.13, 118.33, 119.24, 121.16, 126.48, 127.36, 128.36, 134.15, 135.42, 138.08, 146.54, 154.19, 160.55, 161.86. MS (EI, 70 eV) (*m/z, %*): 238 (M^+, 100), 199(20), 119 (70), 92 (50), 63 (35), 39 (25). *Anal*. Calcd for $C_{14}H_{10}N_2O_2$ (238): C, 70.58; H, 4.23; N, 11.76%. Found: C, 70.44; H, 4.21; N, 12.01%.

2-(3-Nitrophenyl)quinazolin-4(3*H*)-one (1c). White powder, mp >300 ℃. IR (KBr) υ/cm: 3448, 3075, 2928, 1678, 1608, 1531, 1464. ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 7.55-7.58 (m, 1H, Ar-H), 7.73-7.86 (m, 3H, Ar-H), 8.16 (d, J = 7.5 Hz, 1H, Ar-H), 8.41 (d, J = 7.4 Hz, 1H, Ar-H), 8.59 (d, J = 7.5 Hz, 1H, Ar-H), 9.00 (s, 1H, Ar-H), 12.87 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm): 121.65, 123.13, 126.25, 126.36, 127.61, 128.06, 130.39, 134.43, 134.76, 135.21, 148.4, 148.72, 150.96, 162.61. MS (EI, 70 eV) (*m/z, %*): 267 (M^+, 100), 221 (85), 192 (25), 166 (10), 119 (25), 92 (20). *Anal*. Calcd for $C_{14}H_9N_3O_3$ (267.24): C, 69.92; H, 3.39; N, 15.72%. Found: C, 69.94; H, 3.31; N, 15.51%.

2-(4-Nitrophenyl)quinazolin-4(3*H*)-one (1d). Yellow powder, mp >300 ℃. IR (KBr) υ/cm: 3425, 3085, 2925, 1676, 1593, 1473, 1346. ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 7.54-7.99 (m, 5H, Ar-H), 8.15-8.21 (m, 5H, Ar-H), 12.82 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm): 124.02, 126.34, 127.75, 128.15, 128.46, 129.68, 135.17, 137.95, 148.68, 149.36, 151.05, 162.49. MS (EI, 70 eV) (*m/z, %*): 267 (M^+, 40), 220 (35), 192 (40), 119 (50), 76 (100), 50 (80). *Anal*. Calcd for $C_{14}H_9N_3O_3$ (267.24): C, 69.92; H, 3.39; N, 15.72%. Found: C, 69.89; H, 3.31; N, 15.53%.

2-(4-Methoxyphenyl)quinazolin-4(3*H*)-one (1e). White powder, mp 245-246 ℃. IR (KBr) υ/cm: 3444, 3182, 3093, 2961, 2841, 1681, 1605, 1597, 1522, 1483, 1310. ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 3.83 (s, 3H, OMe), 7.07 (br.s, 2H, Ar-H), 7.47-7.92 (m, 3H, Ar-H), 8.11-8.17 (m, 3H, Ar-H), 12.56 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm): 55.85 (OMe), 114.39, 121.12, 125.22, 126.26, 126.49, 127.6, 129.88, 134.82, 147.4, 149.29, 152.33, 162.29. MS (EI, 70 eV) (*m/z, %*): 252 (M^+, 100), 197 (50), 119 (50), 90 (25), 63 (35). *Anal*. Calcd for $C_{15}H_{12}N_2O_2$ (252.27): C, 71.42; H, 4.79; N, 11.10%. Found: C, 71.54; H, 4.61; N, 11.31%.

2-(2,4-Dimethoxyphenyl)quinazolin-4(3*H*)-one (1f). White powder, mp 206-207 ℃. IR (KBr) υ/cm: 3432, 3094, 3061, 1662, 1610, 1509, 1485, 1438, 1386. ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 3.85 (s, 3H, OMe), 3.89 (s, 3H, OMe), 6.46-6.77 (m, 2H, Ar-H), 7.46-8.19 (m, 5H, Ar-H), 11.82 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm): 55.548, 55.98, 114.51, 118.43, 120.65, 122.23, 125.73, 126.12,

127.11, 127.84, 131.79, 134.34, 137.16, 151.92, 158.73, 162.89. MS (EI, 70 eV) (*m/z, %*): 282 (M^+, 50), 252 (25), 225 (30), 199 (100), 171 (30), 119 (85). *Anal*. Calcd for $C_{16}H_{14}N_2O_3$ (282.29): C, 68.07; H, 5.00; N, 9.92%. Found: C, 68.14; H, 4.91; N, 10.01%.

2-(3,4-Dimethoxyphenyl)quinazolin-4(3*H*)-one (1g). White powder, mp 220-222 ℃. IR (KBr) υ/cm: 3444, 3182, 3093, 2841, 1671, 1605, 1567, 1522, 1483. ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 3.84 (s, 3H, OMe), 3.88 (s, 3H, OMe), 7.11 (d, J = 9.1 Hz, 1H, Ar-H), 7.45-7.51 (m, 1H, Ar-H), 7.63-7.95 (m, 4H, Ar-H), 8.12 (d, J = 9.1 Hz, 1H, Ar-H), 12.43 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm): 56.11 (2 OMe), 111.09, 111.78, 121.13, 121.58, 125.17, 126.28, 126.58, 127.76, 135.00, 148.98, 149.35, 152.02, 152.28 162.81. MS (EI, 70 eV) (*m/z, %*): 282 (M^+, 100), 251 (M^+, 25), 236 (30), 119 (40), 90 (35), 90 (25). *Anal*. Calcd for $C_{16}H_{14}N_2O_3$ (282.29): C, 68.07; H, 5.00; N, 9.92%. Found: C, 68.14; H, 4.91; N, 10.02%.

2-(2,4-Dichlorophenyl)quinazolin-4(3*H*)-one (1i). Pale yellow powder, mp 250 ℃ (decomp.). IR (KBr) υ/cm: 3446, 3205, 1692, 1594, 1466, 1333, 1298. ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 7.56-7.88 (m, 5H, Ar-H), 7.99-8.26 (m, 2H, Ar-H), 12.86 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm): 125.82, 127.18, 127.48, 127.96, 129.17, 129.85, 132.20, 132.64, 132.70, 134.60, 137.46, 147.41, 151.91, 160.28. MS (EI, 70 eV) (*m/z, %*): 290 (M^+, 30), 197 (55), 136 (25), 119 (100), 90 (35). *Anal*. Calcd for $C_{14}H_8Cl_2N_2O$ (291.13): C, 57.76; H, 2.77; N, 9.62%. Found: C, 57.81; H, 2.71; N, 9.71%.

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