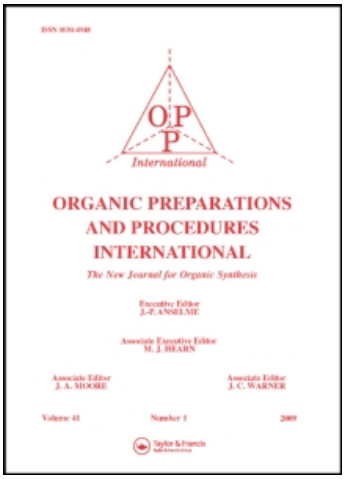

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REINVESTIGATION OF THE SYNTHESIS OF 2-BENZYL-3-ARYL-QUINAZOLIN-4-[3*H*]-ONES. AN IMPROVED MULTI-COMPONENT PROCEDURE USING MICROWAVES

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OPPI BRIEFS

REINVESTIGATION OF THE SYNTHESIS OF 2-BENZYL-3-ARYL-QUINAZOLIN-4-[3*H*]-ONES. AN IMPROVED MULTI-COMPONENT PROCEDURE USING MICROWAVES†

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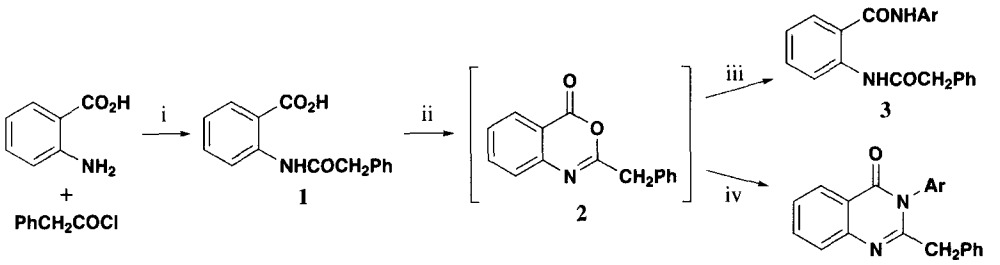
4[3H]-Quinazolinones have wide ranging biological activities[1,2] and have been used as anti-convulsant drugs with anti-inflammatory, analgesic and hypnotic properties.[3-5] Some 4[3H]-quinazolinones also display CNS, anti-fungal, antibacterial and anti-microbial activities[6,7] and are also useful as anti-tumor agents.[8] 2,3-Disubstituted quinazolones have been associated with antiviral, antibacterial and antifungal activity.[9,10]

An earlier reported conventional synthesis of 2,3-disubstituted quinazolin-4(3*H*)-ones (**4**) involves two steps,[11] cyclodehydration of 2-benzamidobenzoic acid (**1**) with excess acetic anhydride under anhydrous conditions to give benzoxazin-4-one (**2**) followed by reflux of **2** with amines in glacial acetic acid or pyridine.[12] The products were obtained in moderate yields and the reaction requires 10-12 h refluxing. In view of our desire to synthesize a series of 2,3-disubstituted quinazolones (**4**) with pharmacophoric groups and to establish structure-activity relationship in quinazolones, the condensation of benzoxazin-4-one with substituted anilines was studied. While *m*- and *p*-substituted anilines gave the expected products **4**, the *o*-substituted anilines afforded the intermediate *o*-acylaminobenzanilides (**3**), in contrast to earlier report of Mishra *et al.*[11] The synthesis of a compound with the same substituent (R = *o*-nitrophenyl) was repeated under the conditions specified by Mishra *et al.*, and the products were identified as **3** and not as quinazolones (**4**). Hence, the method was found to be unsuitable for the reaction involving *o*-substituted anilines. This observation is in agreement with the report of Zentmyer *et al.*[13]

Microwave irradiation is an alternate energy source whose popularity and synthetic utility in organic chemistry has increased considerably in recent years.[14] Solvent-free conditions are especially suitable for microwave irradiation. A literature survey reveals examples of certain reactions, which do not occur under conventional conditions but become possible under microwave irradiation.[15] Recently multi-component reactions (MCRs) constitute an especially attractive synthetic strategy for the rapid and efficient generation of libraries of compound.[16]



a) Ar = 2-NO_2•C_6H_4; b) Ar = 2, 6-Cl_2•C_6H_3; c) Ar = 2-CH_3•C_6H_4

i) Stirring (room temp.); ii) Ac_2O, Δ; iii) HOAc, *o*-substituted anilines; iv) HOAc, *m*- and *p*-substituted anilines

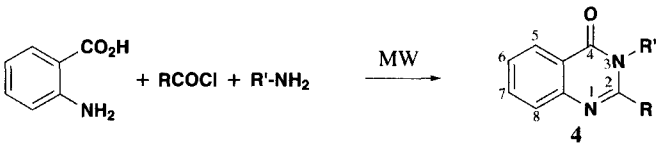
Scheme 1

The synthesis of 4[3*H*]-quinazoline-4-one core nucleus using microwaves has been reported from the reaction of anthranilic acid with formamide.[17] Herein we describe an improved procedure using the multi-component reaction of anthranilic acid, acid chlorides and amines under microwave irradiation using neat reaction conditions. The results showed that the reaction occurred in a shorter time with facile work-up and thus provides a general route to the synthesis of 4[3*H*]-quinazolinones (**4**) with a variety of amines and acid chlorides.

Table 1. Physical and Analytical Data of Compounds **(3a-c)**

Cmpd	Yield (%)	mp (°C)	Elemental Analysis (Found) C	H	N
3a	65	166/165[11]	67.19(67.01)	4.56(4.55)	11.19(11.17)
3b	68	174-176	63.17(63.00)	4.04(4.03)	7.02(7.01)
3c	62	170-172	76.72(76.52)	5.85(5.82)	8.13(8.11)

The formation of *o*-acylaminobenzanilide **3a-c** and 4(3*H*)-quinazoline-4-one **4a-n** was confirmed on the basis of spectral studies. The IR spectra of **3a-c** displayed characteristic bands at 3360-3400 (NH), 1700 and 1680 (both C=O) cm^{-1}. IR spectra of quinazolones **4a-n** showed only one carbonyl band at 1700 and 1605-1610 (C=N) cm^{-1} confirming the ring closure in all compounds. The detailed spectral data of compound **3a-c** and **4a-n** are given in *Table 3*. The mass



a) R = $PhCH_2$, R' = 2-NO_2•C_6H_4; b) R = $PhCH_2$, R' = 2,6-Cl_2•C_6H_3; c) R = $PhCH_2$, R' = 2-Me•C_6H_4; d) R = $PhCH_2$, R' = 3-Cl•C_6H_4; e) R = $PhCH_2$, R' = 4-Me•C_6H_4; f) R = Ph, R' = 4-Cl•C_6H_4; g) R = Ph, Ar = 2-Cl•C_6H_4; h) R = Ph, R' = 4-Br•C_6H_4; i) R = Ph, R' = 3-CF_3, 4-Cl•C_6H_3; j) R = CH_3, R' = 2-F•C_6H_4; k) R = CH_3, R' = 4-NO_2•C_6H_4; l) R = Ph, R' = C_2H_5; m) R = Ph, R' = 3-HO•C_6H_4; n) R = Ph, R' = 4-CH_3O•C_6H_4

Scheme 2

spectrum of representative compounds **3a** and **4a** exhibited the molecular ion peaks at m/z 375 and 357 (100%) which correspond to the molecular weight of compounds **3a** and **4a,** respectively.

Table 2. Physical and Analytical Data of Compounds **(4a-n)**

Cmpd	Yield (%)	Time (min/hs)	mp (°C)	Elemental Analysis (Found) C	H	N
4a	88	5	156-157	70.58(70.39)	4.23(4.22)	11.76(11.73)
4b	91	6	124-126	66.16(65.96)	3.70(3.71)	7.35(7.33)
4c	93	5	116-118	80.96(80.74)	5.56(5.54)	8.58(8.60)
4d	90[a]/61[b]	4[a]/12[b]	164-166	72.73(72.52)	4.36(4.37)	8.08(8.06)
4e	92[a]/60[b]	5[a]/12[b]	110-112	80.96(80.74)	5.56(5.55)	8.58(8.56)
4f	92	5	183-185	72.18(72.00)	3.94(3.93)	8.42(8.40)
4g	90	4	140-142	72.18(72.38)	3.94(3.93)	8.42(8.44)
4h	91	5	220-222	63.68(63.48)	3.47 (3.46)	7.43(7.41)
4i	89	4	170-172	62.93(62.75)	3.02(3.01)	6.99(6.97)
4j	90	4	225-227	70.86(70.65)	4.36(4.35)	11.02(10.98)
4k	90	5	112-114[12]	64.05(64.20)	3.94(3.93)	14.94(14.90)
4l	92	4	230-231	76.78(76.58)	5.64(5.63)	11.19(11.16)
4m	89	5	235-237	76.42(76.20)	4.49(4.50)	8.91(8.93)
4n	90	5	303-305	76.81(76.60)	4.91(4.92)	8.53(8.51)

a) Yield and time (min) correspond to microwave method. b) Yield and time (hs) correspond to conventional method.

EXPERIMENTAL SECTION

Mps were determined in open glass capillary and are uncorrected. IR spectra were recorded on a Perkin-Elmer (model-577) (KBr). ^{1}H NMR and ^{13}C NMR were recorded on Jeol model FX 90Q and Bruker-DRX-300 using $CDCl_3$ as solvent and TMS as an internal reference at 89.55 and 75.47 MHz, respectively. Mass spectra of representative compounds were obtained on Kratos 50 mass spectrometer at 70 eV. The purity of all compounds was checked by TLC using silica gel 'G' coated glass plates and benzene-ethylacetate (8;2) as eluent. The microwave-induced reactions were carried out in BMO-700T modified multimode oven fitted with a condenser and a magnetic stirrer.

Synthesis of 2-Phenylmethyl-3-(2-nitrophenyl)quinazolin-4(3*H*)-one(4a).- To an equimolar mixture of anthranilic acid (2 mmol) and phenylacetyl chloride (2 mmol) contained in an Erlenmeyer flask fitted with a condenser, 2-nitroaniline (2 mmol) was added slowly. The flask was then placed in the microwave oven and irradiated for 5 min (TLC) at 640 watts. The reaction mixture was cooled at room temperature to give a solid, which was recrystallized from ethanol to give **4a**. All compounds **4b-n** listed in *Table 1* were synthesized similarly in high yields and

reduced time. In case of reaction of *m*-amino- phenol, the sticky product obtained after irradiation of reaction mixture was triturated with pet-ether and recrystallized from ethanol to give crystals of **4m**.

Table 3. ^{1}H and ^{13}C NMR Spectra of Compounds (**3a-c**) and (**4a-n**)

Cmpd	^{1}H NMR (δ)	^{13}C NMR (δ)
3a	4.21 (s, 2H, C<u>H</u>$_2$Ph), 6.90-8.21 (m, 13H, Ar-H), 8.99 & 10.12 (two bs, two NH, D_2O exchangeable)	170.2, 169.2 (two C=O), 142.8-119.2 (aromatic carbons), 45.9 (CO-<u>C</u>H$_2$)
3b	4.24(s, 2H, C<u>H</u>$_2$Ph), 6.98-8.18(m, 12H, Ar-H), 9.01 & 10.15(two bs, two NH, D_2O exchangeable)	171.1, 168.2 (two C=O), 145.2-118.9 (aromatic carbons), 44.8 (CO-<u>C</u>H$_2$)
3c	2.24(s, 3H, CH_3), 4.22(s, 2H, C<u>H</u>$_2$Ph), 6.92-8.16(m, 13H, Ar-H), 8.96 & 10.12 (two bs, two NH, D_2O exchangeable)	169.8, 168.0 (two C=O), 141.2-117.7 (aromatic carbons), 44.1 (CO-<u>C</u>H$_2$), 19.2 (CH_3)
4a	3.93 (s, 2H, C<u>H</u>$_2$Ph), 6.85-7.15 (m, 5H CH$_2$<u>Ph</u>), 7.20-8.15 (m, 7H, Ar-H), 8.36 (dd, 1H, 5-H)	169.5 (C=O), 157.1 (C=N), 142.8-119.2 (aromatic carbons), 23.4 (<u>C</u>H$_2$Ph)
4b	3.93 (s, 2H, C<u>H</u>$_2$Ph), 6.89-7.16 (m, 5H CH$_2$<u>Ph</u>), 7.22-8.10 (m, 6H, Ar-H), 8.35 (dd, 1H, 5-H).	168.9 (C=O), 156.2 (C=N) 144.5-118.4 (aromatic carbons), 24.4 (<u>C</u>H$_2$Ph)
4c	2.21 (s, 3H, CH_3), 3.90 (s, 2H, C<u>H</u>$_2$Ph), 6.86-7.18 (m, 5H CH$_2$<u>Ph</u>), 7.20-8.14 (m, 7H, Ar-H), 8.34 (dd, 1H, 5-H)	170.1 (C=O), 157.3 (C=N) 141.5-116.4 (aromatic carbons), 24.6 (<u>C</u>H$_2$Ph), 18.2 (CH_3)
4d	3.93 (s, 2H, C<u>H</u>$_2$Ph), 6.85-7.20 (m, 5H CH$_2$<u>Ph</u>), 7.23-8.16 (m, 7H, Ar-H), 8.30 (dd, 1H, 5-H)	169.5 (C=O), 156.8 (C=N), 143.5-117.4 (aromatic carbons), 25.1 (<u>C</u>H$_2$Ph)
4e	2.18 (s, 3H, CH_3), 3.92 (s, 2H, C<u>H</u>$_2$Ph), 6.88-7.16 (m, 5H CH$_2$<u>Ph</u>), 7.20-8.10 (m, 7H, Ar-H), 8.31 (dd, 1H, 5-H)	168.8 (C=O), 156.9 (C=N) 142.5-118.2 (aromatic carbons), 24.8 (<u>C</u>H$_2$Ph), 18.8 (CH_3)
4f	6.86-7.41 (m, 5H, Ph), 7.50-8.01 (m, 7H, Ar-H), 8.12 (dd, 1H, 5-H)	170.6 (C=O), 157.2 (C=N), 143.2-118.2 (aromatic carbons)
4g	6.89-7.44 (m, 5H, Ar-H), 7.48-8.09 (m, 7H, Ar-H), 8.17 (dd, 1H, 5-H)	171.2 (C=O), 156.8 (C=N) 144.5-119.2 (aromatic carbons)
4h	6.91-7.48 (m, 5H, Ar-H), 7.51-8.12 (m, 7H, Ar-H) 8.20 (dd, 1H, 5-H)	172.4 (C=O), 158.1 (C=N), 143.6-120.3 (aromatic carbons)
4i	6.84-7.38(m, 5H, Ar-H) and 7.45-7.01 (m, 6H, Ar-H), 8.10(dd, 1H, 5-H)	----
4j	.96 (s, 3H, CH_3), 6.51-7.88 (m, 7H, Ar-H), 7.99 (dd, 1H, 5-H)	171.8 (C=O), 159.2 (C=N), 142.8-119.8 (aromatic carbons), 17.0 (CH_3)
4k	.98 (s, 3H, CH_3), 6.54-7.92 (m, 7H, Ar-H), 8.05 (dd,1H, 5-H)	----

Table 3. Continued...

Cmpd	^{1}H NMR (δ)	^{13}C NMR (δ)
4l	1.22 (t, 3H, CH_3), 3.24 (q, 2H, CH_2), 7.29-7.90 (m, 8H, Ar-H), 8.14 (dd, 1H, 5-H)	170.8 (C=O), 158.3 (C=N), 142.8-124.2 (aromatic carbons), 33.4 (CH_2), 12.8 (CH_3)
4m	8.78 (s, 1H, OH, D_2O exchangeable), 6.71-7.47 (m, 5H, Ar-H) and 7.52-7.99 (m, 7H, Ar-H), 8.19 (dd, 1H, 5-H)	172.1 (C=O), 160.2 (C=N), 145.8-122.1 (aromatic carbons)
4n	4.24 (s, 1H, OCH_3), 6.88-7.38 (m, 5H, Ar-H), 7.48-8.09 (m, 7H, Ar-H), 8.17 (dd, 1H, 5-H)	171.8 (C=O), 161.8 (C=N), 143.8-120.8 (aromatic carbons), 52.4 (OCH_3)

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