One-pot Three-component Synthesis of 2-Substituted 4-Aminoquinazolines

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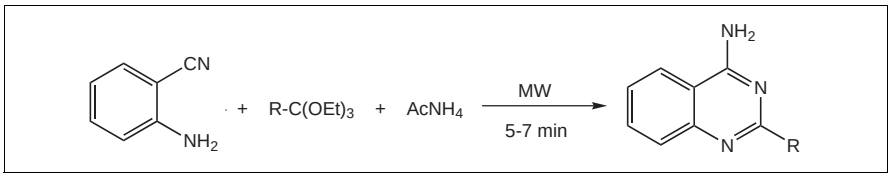

A facile and rapid synthesis of the title compounds via one-pot reaction of 2-aminobenzonitrile, orthoesters and ammonium acetate under solvent-free and microwave condition is described.

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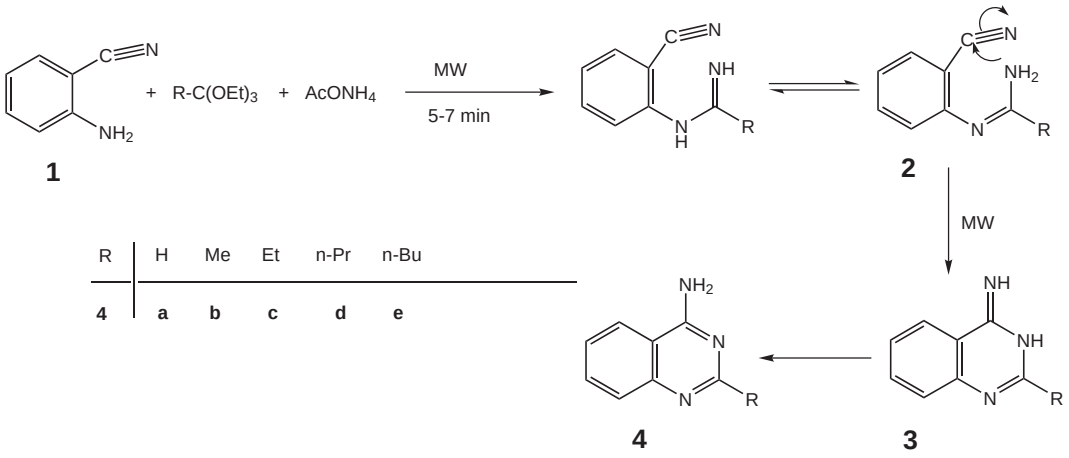
Introduction.

The quinazoline ring system is a commonly encountered structural core in a number of natural and synthetic molecules with a wide range of biological activities [1]. Many of the quinazoline derivatives are known to exhibit anti-inflammatory [2], anthelmintic [3], analgesic [4], *CNS*-depressant [5], and anticonvulsive [6] activities. Metolazone and quinethazone are two quinazoline-based drugs which are used currently as diuretics in medicine [7]. These interesting properties have continually attracted many efforts to the synthesis [8], including microwave-assisted synthesis [9], and pharmacological screening of quinazolines. During these vast investigations 4-quinazolinamine moiety has been identified as a biologically active scaffold [10]. As a result now prazosin, a 4-quinazolinamine-based drug, is offered for treatment of hypertension, known to act by vasodilatation [7]. Specially, some quinazolinamines have shown anti-tumor properties, for example, trimetrexate (*TMTX*) recently has achieved clinical evaluations for cancer chemotherapy [11].

In the course of our investigations on the synthesis of substituted quinazolin-4(3*H*)-ones under microwave irradiation recently we devised a solvent-free three-component reaction employing ammonium acetate and orthoester, as *N*-3 and *C*-2 supplying reactants, in cyclocondensation with anthranilic acid for construction of quinazolin-4(3*H*)-one ring system [12]. In continuation, and in order to extend the scope of the method, we aimed to examine the possibility of synthesis a series of the 4-aminoquinazoline derivatives under such mild conditions.

Herein, we wish to describe that a mixture of 2-aminobenzonitrile, orthoester, and ammonium acetate strongly absorbs microwave energy to afford the products, 2-alkyl-4-aminoquinazolines **4a-e**, in a few minutes and good yields. To our knowledge there has been no report of the use of ammonium acetate as a separate synthon for *N*-3 in a synthesis of 4-aminoquinazolines.



Results and Discussion.

Representative examples of 2-alkyl-4-aminoquinazolines that have been successfully prepared by this method and their yields are given in the Table. It is also possible

to effect the reaction in refluxing ethanolic solution or by heating the reaction mixture in the absence of solvent. The results of examining these conventional heating methods are also collected in the Table. A comparison of the results of performing the reaction in refluxing absolute ethanol with those obtained under solvent-free microwave conditions, indicates a preference for the later method. Our attempt to obtain 2-phenyl-4-aminoquinazoline in this way using trimethyl orthobenzoate was unsuccessful.

Table

Physical data for compounds **4a-e**

Entry	R	[a] Yields (%) of reaction in ethanol (Time)	[a] Yields (%) of reaction without solvent		Mp / °C	Lit. mp / °C
			Microwave (Time)	Classical reflux (Time)		
4a	H	79 (180 min)	89 (5 min)	92 (30 min)	270 – 272	266 – 268 [13]
4b	Me	71 (240 min)	82 (7 min)	83 (45 min)	222 – 224	225 – 227 [14]
4c	Et	81 (240 min)	87 (7 min)	90 (80 min)	219 – 220	225 [15]
4d	n-Pr	77 (240 min)	84 (7 min)	88 (80 min)	217 – 218	214 – 216 [14]
4e	n-Bu	80 (240 min)	89 (7 min)	90 (80 min)	208 - 210	–

[a] Yields of separated products, based on 2-aminobenzonitrile.

Although an excess of orthoester is necessary to diminish the side reactions, involving 2:1 condensation of 2-aminobenzonitrile with orthoester, the solventless conventional heating method needs even more orthoester both to act in place of solvent and to improve the yields. Perhaps, the prominent feature of most microwave conditions is the *in situ* quick conversion of microwave to heat and possibly producing more homogeneous thermal profile than the conventional heating method [16]. So, in many such cases, the role of solvent as heat dispersant is no longer needed. The so-called solvent-free reactions are eco-friendly and in view of green-chemistry's desire for avoiding the solvent hazards, are in demand.

The majority of synthetic routes to 4-quinazolinamines involve the S_NAr type reaction of proper amines at 4-position of suitably substituted quinazolines [17]. Among other methods encountered in literature, the cyclization of aromatic or aliphatic nitriles with 2-aminobenzonitrile was a frequent reaction that performed in various conditions to afford the 4-aminoquinazolines. In one of them that performed in a nearly neutral condition, despite the prolonged heating at elevated temperatures, the cyclization gave low yields of 2-alkyl and 2-aryl derivatives [18]. Strong bases [19] and acids [20] proved to facilitate the reaction; however, there are scarce examples of synthesis of the 2-alkyl derivatives in basic conditions. To this end, one therefore recognizes the simple method presented here valuable, not only for promoting the existing routes but also for the mild *p*H condition that it adopts.

The mechanism of reaction is better conceived as initial formation of the intermediate amidine 2, which undergoes following cyclization through addition of the amino moiety to the nitrile group. The thus formed 4(3*H*)-iminoquinazoline 3 subsequently tautomerizes to the desired product 4. Though, addition of amines to nitrile group requires a strenuous condition with the aid of strong Lewis acids [21], here the intramolecular analogue process take place with some facilities in nearly neutral media.

All of the products except **4e** are known compounds and their melting points, ir and ^{1}H nmr spectral data are in good agreement with those cited in the literature, as well as the authentic samples prepared from the previously reported methods. The spectral data of **4c** were lacking in the literature, so they are given with **4e** under experimental section. In the ir spectrum of **4e** the N-H bending vibration of amino group is observed as a strong and distinct peak at 1675 cm^{-1}, while the N-H stretching vibrations are perceived as weak bands at 3270 and 3450 cm^{-1}. The ^{1}H nmr spectrum of **4e** in dimethyl sulfoxide-d_6 solution revealed the characteristic downfield shift of C_5-H proton at 8.17 ppm as a doublet along with resonances which readily assigned to other aromatic protons. Careful ^{1}H nmr spectral checking displayed NH_2 peak, as being hidden exactly under a triplet raised from C_7-H resonances, at 7.69 ppm. The NH_2 and C_5-H peaks shift to upper fields on taking the spectrum in deuteriochloroform (to 5.57 and 7.82 ppm, respectively). There are also four sets of multiplets corresponding to resonances of aliphatic protons. The ^{13}C nmr spectrum of **4c** and **4e** showed the expected resonances in agreement with the structure of products. Partial assignments of these resonances are given in experimental section. The mass spectrum of **4c** displayed M^+-1 as the base peak, but for **4e** the base peak is a fragment tallying to

4b molecular ion. The intensity of this fragment can be evidenced to the pronounced McLafferty-type fragmentation of *n*-butyl chain. The pattern of fragmentation suggests scission of alkyl substituent as a major early step associated with rupture in the pyrimidine ring that is responsible for the predominant loss of cyanides.

In summary, we have introduced here a convenient and solvent-free route to the synthesis of 4-aminoquinazolines using simple starting materials. The present method also carries the advantages that it performs in one-pot and nearly neutral condition.

EXPERIMENTAL

Melting points are uncorrected and were measured on a Mettler FP5 melting point apparatus. Elemental analyses (C, H, N) were conducted using a Heraeus CHN-O-Rapid analyzer. The experimental results were found to be in good agreement with the calculated values. IR spectra were obtained in potassium bromide wafers on Shimadzu IR-470 spectrometer. ^{1}H and ^{13}C nmr spectra were measured with a Bruker DRX-500 AVANCE instrument with dimethyl sulfoxide-d_6 as solvent at 500.1 and 125.7 MHz, respectively. Mass spectra were recorded on an Agilent 5973 mass spectrometer operating at an ionization potential of 70 eV. Microwave irradiations were carried out in a 1000 Watt oven at 2450 MHz. Chemicals were obtained from Fluka (Buchs, Switzerland) and were used without further purification.

General Procedure Under Microwave Irradiation.

A mixture of 2-aminobenzonitrile (0.59 g, 5 mmol), orthoester (12 mmol in each case) and ammonium acetate (0.77 g, 10 mmol) was placed in a 50 mL beaker. The beaker was covered with a stemless funnel and then irradiated in the microwave oven for 2 minutes with a power of 180 Watt, (for **4a**; 2 minutes at 120 Watt). After a cooling time of about 5 minutes to room temperature the beaker was irradiated again for 5 minutes at 210 Watt, (for **4a**; 3 minutes at 180 Watt). The resultant residues were crystallized from aqueous ethanol (80%).

2-Butyl-4-aminoquinazoline (**4e**).

This compound was obtained as colorless crystals (aqueous ethanol), mp 208-210°; ir (potassium bromide): 3450, 3270, 1675 NH, 1571, 1553 C=N, 1500, 1613 C=C cm^{-1}; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 8.17 (d, 1H, 5-H), 7.69 (t, 3H, 7-H and NH_2), 7.56 (d, 1H, 8-H), 7.39 (t, 1H, 6-H), 2.66 (t, 2H, α-CH_2), 1.73 (m, 2H, β-CH_2), 1.34 (q, 2H, γ-CH_2), 0.89 (t, 3H, CH_3) ppm; ^{13}C nmr (dimethyl sulfoxide-d_6): δ 167.7 (C-4), 162.7 (C-2), 151.1 (C-8_a), 113.6 (C-4_a), 133.3, 127.8, 125.2, 124.2 (4 CH), 39.7 (α-$^{13}CH_2$), 31 (β-$^{13}CH_2$), 22.9 (γ-$^{13}CH_2$), 14.7 ($^{13}CH_3$) ppm; ms: *m/z* 201 (M^+), 186 (M^+ -CH_3), 172 (M^+ -CH_2CH_3), 159 (M^+ -C_3H_6), 119 (M^+ -C_4H_9CN).

Anal. Calcd. for $C_{10}H_{11}N_3$: C, 69.34; H, 6.40; N, 24.26. Found: C, 69.4; H, 6.4; N, 24.2.

General Procedure Under Classical Heating in Ethanol.

A stirred mixture of 2-aminobenzonitrile (0.59 g, 5 mmol), orthoester (12 mmol in each case), ammonium acetate (0.77 g, 10 mmol) in absolute ethanol (8 mL) was refluxed gently and the reaction progress was followed by tlc (*n*-hexane:EtOAc: CH_3OH, 3:3:1). After the required time that 2-aminobenzonitrile considerably diminishes (see Table) the reaction mixture was concentrated by evaporation of solvent *in vacuo*, cooled and the white precipitate thus obtained was collected by filtration and then recrystallized in aqueous ethanol (80%).

General Procedure Under Classical Heating, Without Solvent.

A stirred mixture of 2-aminobenzonitrile (0.59 g, 5 mmol), orthoester (16 mmol in each case), and ammonium acetate (0.77 g, 10 mmol) was refluxed gently in oil bath at 120 °C. The reaction progress was followed by tlc (*n*-hexane:EtOAc: CH_3OH, 3:3:1). After the required time that 2-aminobenzonitrile diminishes to a trace (see Table) the reaction mixture was cooled to room temperature and the white solid thus obtained was washed with 5 mL of water and then recrystallized in aqueous ethanol (80%).

2-Ethyl-4-aminoquinazoline (**4c**).

This compound was obtained as colorless crystals (aqueous ethanol), mp 219-220°, lit. mp 225° [15]; ir (potassium bromide): 3443, 3250, 1670 NH, 3065, 2952 CH, 1612, 1495 C=C, 1568, 1551 C=N cm^{-1}; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 8.19 (d, 1H, 5-H), 7.69 (t, 3H, 7-H and NH_2), 7.62 (d, 1H, 8-H), 7.39 (t, 1H, 6-H), 2.70 (q, 2H, CH_2), 1.27 (t, 3H, CH_3) ppm; ^{13}C nmr (dimethyl sulfoxide-d_6): δ 168.5 (C-4), 162.8 (C-2), 151.1 (C-8_a), 133.4, 127.8, 125.3, 124.3 (4 CH), 113.7 (C-4_a), 33.1 (CH_2), 13.5 (CH_3) ppm; ms: *m/z* 173 (M^+), 172 (M^+ -1), 155 (172 -NH_3), 145 (172 -HCN), 127, 118 (M^+ -C_2H_5CN).

Anal. Calcd for $C_{12}H_{15}N_3$: C, 71.61; H, 7.51; N, 20.88. Found: C, 71.6; H, 7.5; N, 20.8.

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