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Base mediated synthesis of 2-aryl-2,3-dihydroquinazolin-4(1*H*)-ones from 2-aminobenzonitriles and aromatic aldehydes in water†

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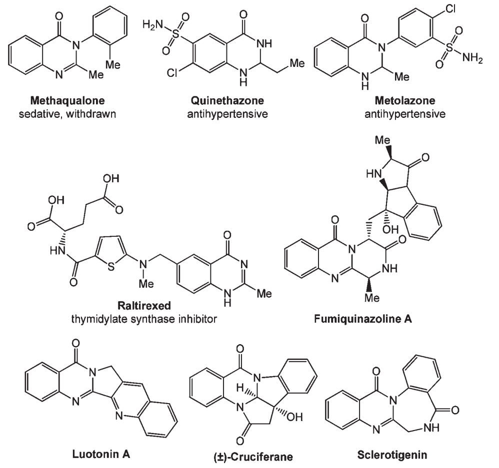
An environmentally friendly and mild procedure to obtain 2,3-dihydroquinazolin-4(1*H*)-ones from 2-aminobenzonitriles and aromatic aldehydes has been developed. The reactions took place in water with inorganic base (K_3PO_4) as the only promoter. Various desired products have been prepared in moderate to good yields under identical conditions. Further transformation of dihydroquinazolinones to quinazolinones was carried out as well with TBHP as the oxidant.

Since the first synthesis of a heterocyclic compound, pyridine, by W. Ramsey in 1877,[1] numerous synthetic routes have been developed to obtain these nitrogen-containing structures.[2] Many biological processes involve these heterocycles as markers or messenger molecules and an array of pharmaceuticals and agrochemicals based on those chemicals have been reported during the past few decades. In this context, 2,3-dihydroquinazolinones as well as the oxidized form, the quinazolinones, represent an important class of substances with a wide range of bioactivities such as thymidylate synthase inhibition, antihypertensive effects and sedative effects.[3] A selection of bio-active quinazolinone derivatives are shown in Scheme 1. Notably, these compounds are relevant building blocks in organic synthesis to form more complex structures such as natural products like luotonin A, sclerotigenin, fumiquinazoline A or (±)-cruciferane.

Based on this wide range of applications of dihydroquinazolinones and their analogues, many pathways for the synthesis of this alkaloid like structure have been described. For example, Rostamizadeh *et al.* reported in 2008 about the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones from isatoic anhydride and aromatic aldehydes under solvent free conditions using catalytic amounts of iodine.[4] Another synthetic strategy to give different 2-substituted dihydroquinazolinones was published by Bunce and co-workers using 2-nitrobenzamides and carbonyl compounds as substrates with iron powder as the promoter.[5] More recently, Kesavan and Prakash reported in 2012 about the enantioselective synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones from 2-aminobenzamides with aldehydes using Sc(III) as a catalyst.[6] Likewise, Wang and co-workers developed a copper-catalyzed method to yield 2-thioxo-dihydroquinazolinones starting from 2-bromobenzamides and isothiocyanates.[7] Additionally, Cheng *et al.* reported about the asymmetric synthesis of dihydroquinazolinones using (*S*)-TRIP as the catalyst.[8] Furthermore, Li *et al.* published in 2010 about the formation of 2,3-dihydroquinazolin-4(1*H*)-ones from 2-aminobenzonitriles and carbonyl compounds using $ZnCl_2$ as a Lewis acid in refluxing DMF.[9] On the other hand, procedures for quinazolin-4(1*H*)-ones preparation based



Scheme 1 Selected examples of biologically active quinazolinone derivatives.

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† Electronic supplementary information (ESI) available: General procedure, NMR data and spectra, X-ray data. CCDC 975991. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3ob42434k

on different catalysts and substrates were developed as well.[10–13]

As a part of our contribution to the heterocyclic building block synthesis, we wish to present herein a convenient and facile way to obtain 2,3-dihydroquinazoline-4(1*H*)-ones. A range of different substituted compounds were obtained from 2-aminobenzonitriles and different aldehydes *via* a base mediated tandem imine condensation–cyclization reaction. Interestingly, the reactions were carried out only with the addition of a base and using water as a cheap, environmentally friendly and harmless solvent.[14] No additional catalyst was needed and the desired products were produced in good yields. Additionally, a two-step-one-pot oxidation to obtain 2-phenyl-quinazolinone was realized without problem.

The model reaction was carried out using simple 2-aminobenzonitrile and 1.2 equiv. of benzaldehyde in water with K_3PO_4 as the base. The desired product was isolated in good yields. Lowering the temperature below 100 °C resulted in a decrease of the yield which can be explained by the solubility of the substrates. The strong base dependency of the activation of the nitrile group leads to the need for an equimolar amount of a promoter. Hence, catalytic amounts of the base did not give any isolatable product at all. Changing the base from K_3PO_4 to KOH resulted in a slight increase of the yield (Table 1, entry 6). The reaction works as well in organic solvents, such as DMF, DMSO, or toluene, but with lower conversion and selectivity.

Two similar structures 2-phenyl-1*H*-benzo[*d*][1,3]oxazin-4(2*H*)-imine (**1**)[15] and 2-phenyl-2,3-dihydroquinazolin-4(*H*)-one (**2**)[9] have been reported as the products from the reaction between 2-aminobenzonitrile and benzaldehyde under similar reaction conditions respectively (Fig. 1). Regarding the uncertainty of the structure, we paid special attention to the structure analysis of the model substance.

Since mass spectroscopic studies as well as 1D-NMR experiments did not give the needed information on the present structure, we focused on 2D-NMR studies. At first, the couplings of the two amino-protons with the benzylic hydrogen atom (pos. 2) are visible in the H–H-COSY spectrum. Additionally, the interaction of these three nuclei can be confirmed by NOESY experiment. Furthermore, the correlation of the amino-protons with the hydrogens (Fig. 2) attached to the phenyl ring (pos. 10 and 14) can be observed. Also, no interaction of the amino proton (3) with the quinazolinone ring can be detected. This indicates that dihydroquinazolinone but not the isomeric imino benzoxazine is the final product. The structure has also been confirmed by X-ray analysis (Fig. 2) of the analogue isopropyl substituted compound (3). The N(1)–C(1) bond (1.454 Å) and the C(1)–N(2) bond (1.464 Å) show significant single bond lengths. Additionally, intermolecular N(1)–H(1A)···O(1) (D–H 0.89(2) Å, H···A 2.17(2) Å, D···A 2.967(13) Å, D–H···A 149.7(13)) and N(2)–H(2)···O(1) (D–H 0.89(2) Å, H···A 2.03(2) Å, D···A 2.918(13) Å, D–H···A 178.8(13)) weak hydrogen bonds can be observed. Since the significant N*H*-signals in the ^{1}H-NMR spectra of all isolated compounds follow the same pattern, it can be assumed that both nitrogen atoms are endocyclic. In addition, gas chromatographic analysis showed the existence of both enantiomers.

Table 1 Influence of the base concentration[a]

Entry	Base	Concentration	Yield[b]
1	K_2CO_3	0.2 M	33%
2	$CsCO_3$	0.2 M	0%
3	K_3PO_4	0.002 M	0%
4	K_3PO_4	0.2 M	73%
5	KOH	0.002 M	0%
6	KOH	0.2 M	75%

[a] 1 equiv. of 2-aminobenzonitrile, 1.2 equiv. of benzaldehyde, base, 5 mL H_2O, 100 °C, 8 h. [b] Isolated yields.

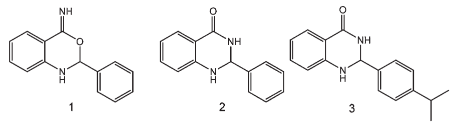


Fig. 1 2-Phenyl-1*H*-benzo[*d*][1,3]oxazin-4(2*H*)-imine (**1**), 2-phenyl-2,3-dihydroquinazolin-4(1*H*)-one (**2**) and *p*-isopropylphenyl-2,3-dihydroquinazolin-4(1*H*)-one (**3**).

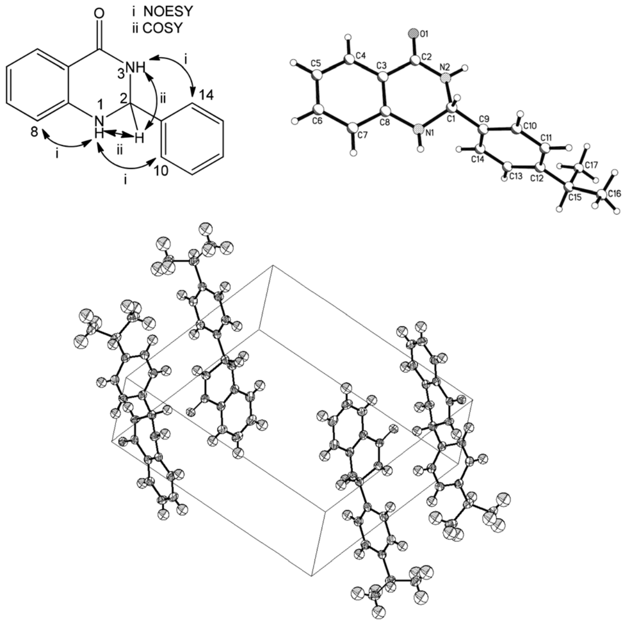
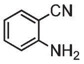
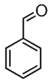
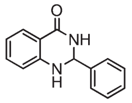
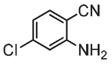
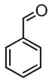
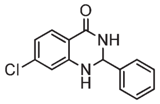
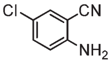
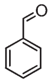
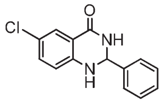
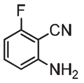
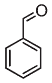
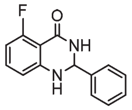
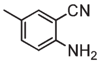
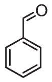
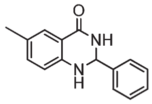
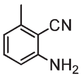
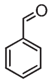
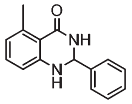
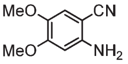
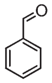
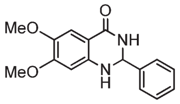
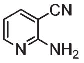
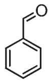
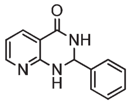
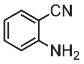
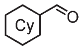
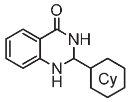
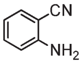
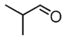
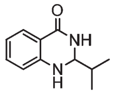
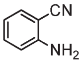
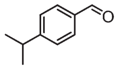
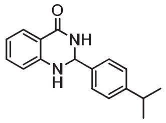
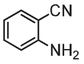
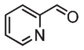
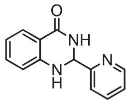
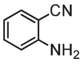
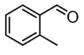
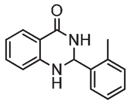
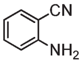
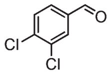
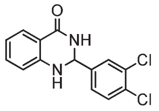
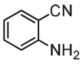
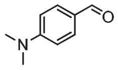
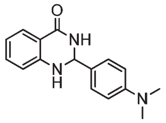


Fig. 2 2D-NMR-coupling pattern of **2**, crystal structure and packing diagram of compound **3**, bond length (Å): O(1)–C(2) 1.2448(14), N(1)–C(1) 1.4542(16), N(2)–C(1) 1.4641(16), N(2)–C(2) 1.3420(15), C(1)–C(9) 1.5123(18), C(2)–C(3) 1.4785(16), C(3)–C(4) 1.3941(17), C(3)–C(8) 1.4044(17), C(4)–C(5) 1.3804(18), C(5)–C(6) 1.390(2), C(6)–C(7) 1.3825(19), C(7)–C(8) 1.4046(18), C(9)–C(10) 1.3780(17), C(9)–C(14) 1.3903(17), C(10)–C(11) 1.3840(18), C(11)–C(12) 1.3857(18), C(12)–C(13) 1.3980(17), C(12)–C(15) 1.5188(18), C(13)–C(14) 1.3859(18), C(15)–C(16) 1.5231(19), C(15)–C(17) 1.534(2).

Afterwards, we investigated the limitations and effects of different substituents on the benzonitrile and the aldehydes, respectively. The substrates scope is shown in Table 2. Many different substituted dihydroquinazolinones can be obtained

Table 2 Synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones[a]

Entry	Amine	Aldehyde	Product 4	Yield[b] (%)
1				75
2				58
3				23
4				41
5				14
6				0
7				43
8				66
9				43
10				64
11				26
12				64
13				0
14				58
15				22

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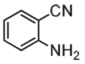
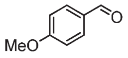
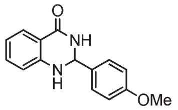
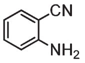
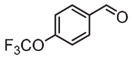
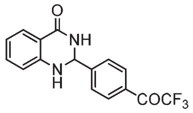
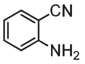
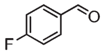
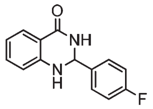
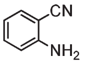
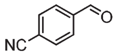
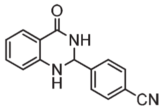
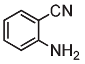
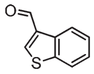
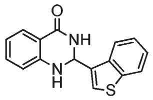
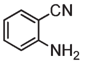
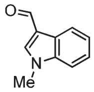
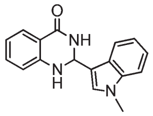
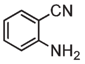
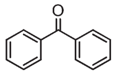
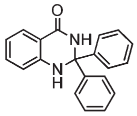
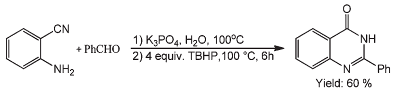
Entry	Amine	Aldehyde	Product 4	Yield[b] (%)
16				80
17				49
18				37
19				60
20				28
21				0
22				0

[a] Reaction conditions: 1 equiv. 2-aminobenzonitriles, 1.2 equiv. aldehydes, 1 equiv. K_3PO_4, 5 mL H_2O, 100 °C, 8 h. [b] Isolated yields.

by this method up to very good yields. Regarding the reaction mechanism, we believe that the first step is the reaction between 2-aminobenzonitrile and benzaldehyde to give the corresponding 2-((hydroxy(phenyl)methyl)amino)benzonitrile. This is followed by base assisted nucleophilic attack of OH^- to the nitrile group to give 2-phenyl-1*H*-benzo[*d*][1,3]oxazin-4(2*H*)-imine as the intermediate which can result in the final product after rearrangement.

Various functional groups are tolerable under these conditions and give the desired products in low to excellent yields. In general, electron withdrawing groups on the aldehyde or the 2-aminobenzonitrile, respectively, led to the decrease of the yields. This can be explained by the reduced solubility of the substrates. Also, methyl-substituents neighboring the cyano-group or the aldehyde function did not give the quinazolinone due to the steric hindrance. The electronic effect may be responsible for the results as well, as the *ortho*-methyl substituent decreases the activity of the nitrile group. This methodology can also be applied to non-α-protic aldehydes such as cyclohexane carboxaldehyde and isobutanal (Table 2, entries 9 and 10). For *N*-methylindole-3-carboxaldehyde, no desired product could be obtained under these conditions. To our delight, the related benzothiophene carboxaldehyde succeeded in giving the dihydroquinazolinone product in 28% yield (Table 2, entry 21). No reaction was detected with benzophenone (Table 2, entry 22). Notably, no column purification was needed for the products isolation. The pure products were isolated by simple filtration.



Scheme 2 Quinazolinone synthesis from benzaldehyde.

Subsequently, we carried out the transformation of 2-phenyl-2,3-dihydroquinazolin-4-(1*H*)-one to quinazolinone. By the addition of 4 equiv. of *tert*-butylhydroperoxide (TBHP) to the crude reaction mixture from 2-phenyl-1,2-dihydroquinazolin-4(1*H*)-one and heating to 100 °C for 6 hours, 2-phenylquinazolinone was obtained in good yield (Scheme 2). Using H_2O_2 or decreasing amounts of oxidant led to less conversion which was monitored by TLC (hexane–ethylacetate 8 : 2).

Conclusions

In conclusion, an interesting and convenient procedure for 2,3-dihydroquinazolin-4(1*H*)-ones synthesis has been developed. The desired products were isolated in good yields. A cheap inorganic base was applied as a promoter and water was used as a green solvent for this transformation. One-pot synthesis of quinazolinone from 2-aminobenzonitrile and benzaldehyde was realized as well by using TBHP as an oxidant. Notably, no column purification was needed; all the products were purified by filtration.

Experimental section

General remarks

Distilled water was used as the solvent. All chemicals were commercially available and were used without further purification. NMR-data were recorded using Bruker ARX 300 and Bruker ARX 400 spectrometers. ^{13}C- and ^{1}H-spectra were referenced to deuterated solvent signals. Peaks were characterized as singlet (s), doublet (d), doublet of doublet (dd), triplet (t), triplet of triplets (tt), quartet (q) and multiplet (m). Gas-chromatography-mass-analysis was performed using an Agilent HP-5890 with an Agilent HP-5973 Mass Selective Detector (EI) and an HP-5-capillary column using helium as a carrier gas. Column-chromatography was carried out using Merck 60 Silica-Gel (0.043–0.06 mm) and distilled solvents were used.

General procedure for the base mediated synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones from 2-aminobenzonitriles and aldehydes

A 25 mL pressure tube was charged with 1 mmol (118 mg) 2-aminobenzonitrile, 1.2 mmol benzaldehyde (122 μL, 127 mg), 1 mmol K_3PO_4 monohydrate (230 mg) and 5 mL water and subsequently sealed. The mixture was heated under stirring at 100 °C for 8 hours. The white precipitate was filtered off under reduced pressure and washed with water. The crude solid was dissolved in the minimum amount of boiling ethylacetate and recrystallized by the addition of *n*-hexane. Filtering and drying of the white solid gave 169 mg (75%) 2-phenyl-2,3-dihydroquinazolin-4(1*H*)-one. ^{1}H-NMR (250 MHz, DMSO-d_6): δ = 8.28 (s, 1H, NH(3)), 7.61 (dd, 1H, ^{3}J = 7.8 Hz, ^{4}J = 1.6 Hz, CH(5)), 7.49 (dd, 2H, ^{3}J = 7.9 Hz, ^{4}J = 1.9 Hz, CH(10 + 14)), 7.45–7.29 (m, 3H, CH(11 + 12 + 13)), 7.24 (ddd, 1H, ^{3}J = 8.1 Hz, ^{3}J = 7.2 Hz, ^{3}J = 1.6 Hz, CH(7)), 7.11 (s, 1H, NH(1)), 6.78–6.72 (m, 1H, CH(8)), 6.71–6.63 (m, 1H, CH(6)), 5.75 (t, 1H, ^{3}J = 1.9 Hz, CH(2)); ^{13}C-NMR (63 MHz, DMSO-d_6): δ = 163.6 (C═O(4)), 147.8 (C_{quart}(8a)), 141.6 (C_{quart}(9)), 133.3 (CH(7)), 128.4 (CH(12)), 128.3 (CH(11 + 13)), 127.3 (CH(5)), 126.8 (CH(10 + 14)), 117.1 (CH(6)), 114.9 (C_{quart}(4a)), 114.4 (CH(8)), 66.5 (CH(2)) ppm; GC/MS: (EI, 70 eV) *m*/*z* (%) = 224 ([M]$^{+}$, 19), 223 (27), 147 (100), 120 (42), 119 (15), 104 (10), 92 (29), 77 (20), 65 (14), 64 (10), 51 (15).

The compounds, entries 7, 11 and 19, Table 1, were furthermore purified by column chromatography (toluene–ethylacetate 1 : 1).

General procedure for oxidation of 2,3-dihydroquinazolin-4(1*H*)-ones to 2-phenyl-quinazolinone

To the crude reaction mixture of the synthesis of 2,3-dihydroquinazolinone, 400 μL TBHP-solution (70% in H_2O, 4 mmol) was added. The mixture was heated under stirring to 100 °C for 6 hours. The conversion was monitored by TLC (hexane–ethylacetate 8 : 2). When no dihydroquinazolinone was found in TLC, the precipitate was filtered off and recrystallized from ethylacetate–hexane, giving 134 mg (60%) 2-phenyl-quinazolinone. ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 12.55 (s, 1H, NH), 8.23–8.13 (m, 3H, CH(7 + 10 + 14)), 7.85 (ddd, ^{3}J = 8.5 Hz, ^{3}J = 7.0 Hz, ^{3}J = 1.6 Hz, CH(5)), 7.77–7.71 (m, 1H, CH(12)), 7.62–7.49 (m, 4H, CH(4 + 6 + 11 + 13)) ppm; ^{13}C-NMR (75 MHz, DMSO-d_6): δ = 162.3 (C═O(4)), 152.4 (C_{quart}(2)), 148.7 (C_{quart}(8a)), 134.6 (CH(7)), 132.8 (C_{quart}(9)), 131.4 (CH-(12)), 128.6 (CH(10 + 14)), 127.8 (CH(11 + 13)), 127.4 CH(6)), 126.6 (CH(7)), 125.8 (CH(5)), 121.0 (C_{quart}(4a)) ppm; MS (EI, 70 eV): *m*/*z* (%) = 222 ([M]$^{+}$, 100), 119 (99), 104 (11), 92 (14), 90 (17), 77 (22), 76 (11), 51 (10).

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