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Glucose as an Eco-Friendly Reductant in a One-Pot Synthesis of 2,3-Dihydroquinazolin-4(1H)-ones

Thiago dos Santos,^[a,b] Caroline Grundke,^[a] Tobias Lucas,^[a] Luca Großmann,^[a] Giuliano Cesar Clososki,^{*,[b]} and Till Opatz^{*,[a]}

Abstract: Carbohydrates such as glucose are an abundant renewable resource that can be employed in synthetic processes as a source of carbon and/or hydrogen to yield products of high economical and biological impact. Herein, we report a versatile and environmentally friendly protocol for the one-pot

synthesis of 2,3-dihydroquinazolin-4(1H)-ones, a privileged scaffold in medicinal chemistry, based on the use of glucose as an eco-friendly reductant in alkaline aqueous medium. This method can be viewed as a blueprint for the development of further one-pot sequences involving glucose as a reductant.

Carbohydrates have found application as building blocks to construct larger saccharidic structures or as scaffolds in combinatorial chemistry.^[1–3] Moreover, they have been employed as abundant renewable carbon sources in the preparation of N-heterocycles^[4,5] and as hydrogen sources in mild and eco-friendly reduction processes.^[6–8] In particular, D-glucose is an extremely abundant natural product which can be easily obtained from lignocellulosic biomass (e.g. wood) via enzymatic treatment or acid hydrolysis.^[9,10] Its reductive properties have even been employed in the generation of hydrogen in alkaline medium.^[11,12] The reductive properties of D-glucose directly reflect its nature as a reduced form of CO₂ produced in the course of photosynthetic water splitting.

Considering the wide variety of pharmaceuticals and other bioactive molecules bearing the 2,3-dihydroquinazolin-4(1H)-one motif (illustrated in Figure 1),^[13–16] the development of protocols for its synthesis is relevant for the area of drug discovery.

One-pot reaction cascades are known to provide considerable economical and ecological advantages over stepwise transformations.^[17] They not only consume less solvent and sometimes also lower quantities of reagents and, most importantly, reduce the number of individual isolation and purification oper-

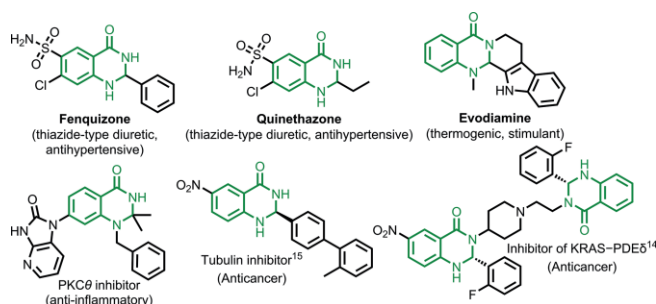


Figure 1. Examples of drugs and bioactive molecules containing the 2,3-dihydroquinazolin-4(1H)-one scaffold.

ations. Thus, we aimed at developing a one-pot reaction involving D-glucose as an eco-friendly reductant. Dihydroquinazolin-ones have been obtained from various precursors for the central bicyclic ring system including 2-aminobenzamides,^[18] isatoic anhydride,^[19] o-halobenzonitriles,^[20] 2-nitrobenzamide,^[21] and 2-aminobenzonitrile.^[22]

In a recent report, Liu and co-workers have employed 2-nitrobenzonitrile as a precursor to 2,3-dihydroquinazolin-4(1H)-ones in a combined reduction/hydration/cyclocondensation sequence. However, they had to employ an excess of di-boronic acid and copper as a catalyst in a water/methanol mixture (Scheme 1).^[23] The intermediate formation of 2,3-dihydroquinazolin-4(1H)-ones from 2-nitrobenzonitrile had also been observed by Kumar and co-workers in the reaction of the latter substrates with phenylglycine in the presence of FeCl₃ and K₂CO₃.^[24] Based on the natural abundance and mild reducing properties of D-glucose, we envisioned the establishment of an eco-friendly transition-metal free alternative one-pot protocol for the synthesis of 2,3-dihydroquinazolin-4(1H)-ones from 2-nitrobenzonitrile in alkaline aqueous solution.

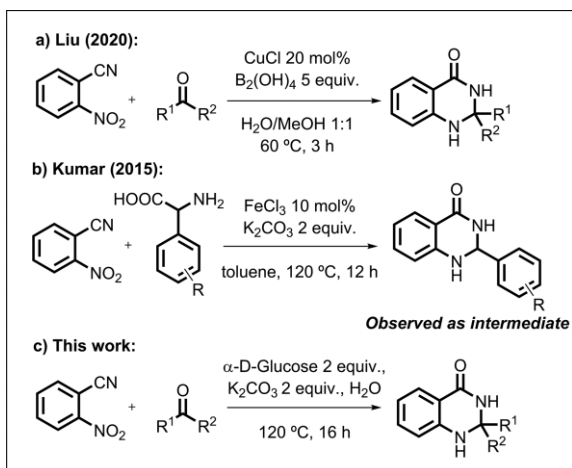
Under avoidance of strong bases such as potassium hydroxide or sodium hydroxide which were regularly applied in reductions with glucose,^[6,12,25] an environmentally benign and inex-

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Scheme 1. Synthetic protocols to furnish 2,3-dihydroquinazolin-4(1H)-ones from 2-nitrobenzonitrile.

pensive base, potassium carbonate,^[26] was chosen in conjunction with an aqueous glucose solution (Table 1). Initially, by setting the temperature to 100 °C and the solvent volume to 0.8 mL with 0.8 mmol (4 equiv.) of the base, both the conversion of the nitroarene into the aniline and the hydration of the cyano group were observed in the formation of 2-aminobenzamide (entry 1, 79 %).^[27] When the reaction was monitored by HPLC-MS, 2-nitrobenzamide and 2-aminobenzonitrile were not observed. Based on the detection of 2-nitrobenzamide at a lower temperature, it can be assumed that the nitrile hydration is the first reaction in the sequence. Reducing the excess of potassium carbonate and varying the amount of glucose (entries 2 and 3) produced a higher yield while running the reaction in air instead of inert atmosphere did not change the outcome (entries 3 and 4). Interestingly, by working with more diluted solutions, a higher yield was obtained (entries 6 and 7) unless the amount of glucose was changed (entry 5). When the reaction was run at 50 °C for three hours or in the absence of

Table 1. Synthesis of 2-aminobenzamide under various conditions.^[a]

Entry	α-D-glucose	Solvent	Base amount	Yield [%] ^[b]
1	2 equiv.	0.8 mL	4 equiv.	79
2	1.5 equiv.	0.8 mL	3 equiv.	87
3	2 equiv.	0.8 mL	2 equiv.	91
4 ^[c]	2 equiv.	0.8 mL	2 equiv.	90
5	1 equiv.	4 mL	2 equiv.	74
6	2 equiv.	4 mL	2 equiv.	94 ^[d]
7	2 equiv.	4 mL	4 equiv.	95
8 ^[e]	2 equiv.	4 mL	4 equiv.	None
9	None	4 mL	2 equiv.	None ^[f]

[a] The time of 3 h, temperature of 100 °C, air as atmosphere, and 0.2 mmol of 2-nitrobenzonitrile apply for all the reactions unless otherwise stated. [b] Dimethyl sulfone was employed as NMR standard for quantification. [c] Argon as atmosphere. [d] Isolated yield: 92 %. [e] The temperature of 50 °C favored the formation of 2-nitrobenzamide (86 % yield, NMR quantification after extraction with AcOEt 3 × 10 mL). [f] Only 2-nitrobenzamide was observed.

glucose, only the hydration of the cyano group of 2-nitrobenzonitrile was observed (entries 8 and 9, respectively). From the reaction described in entry 6 as the established optimum set of conditions, 2-aminobenzamide was isolated in 92 % yield.

Knowing that two equivalents of glucose in water with two equivalents of potassium carbonate satisfactorily led to the conversion of 2-nitrobenzamide into anthranilamide, we then questioned the possibility of using benzaldehyde to afford the imine formation and subsequent 6-*endo-trig*-cyclization furnishing the desired 2,3-dihydroquinazolin-4(1H)-one in a one-pot fashion. Gratifyingly, with one equivalent of benzaldehyde at 100 °C for 16 hours (entry 1, Table 2), 2-phenyl-2,3-dihydroquinazolin-4(1H)-one (**4**) was obtained in 55 % yield along with 2-aminobenzamide (**2**). Increasing the amount of aldehyde favored the conversion of **2** into the imine **3** (entry 2) while setting the temperature to 120 °C with a slight excess of benzaldehyde positively influenced the produced amount of **4** (entry 3). Keeping this temperature but reducing the amount of solvent led to a substantial increase in yield (entry 4, 72 %). This change in conditions was then repeated with 1.5 equivalents of benzaldehyde (entries 5, 6, and 7) with 0.8 mL of water being the optimal observed amount of solvent. Working with a higher amount of the base (entry 10), 1.5 equivalents of glucose with 3 equivalents of potassium carbonate (entry 9), or prolonging the reaction time to 24 hours (entry 8) did not increase the yield. By adopting entry 6 as the optimized set of conditions, **4** was isolated as a white solid in 75 % yield.

Table 2. Optimization of the reaction conditions for the synthesis of 2-phenyl-2,3-dihydroquinazolin-4(1H)-one.^[a]

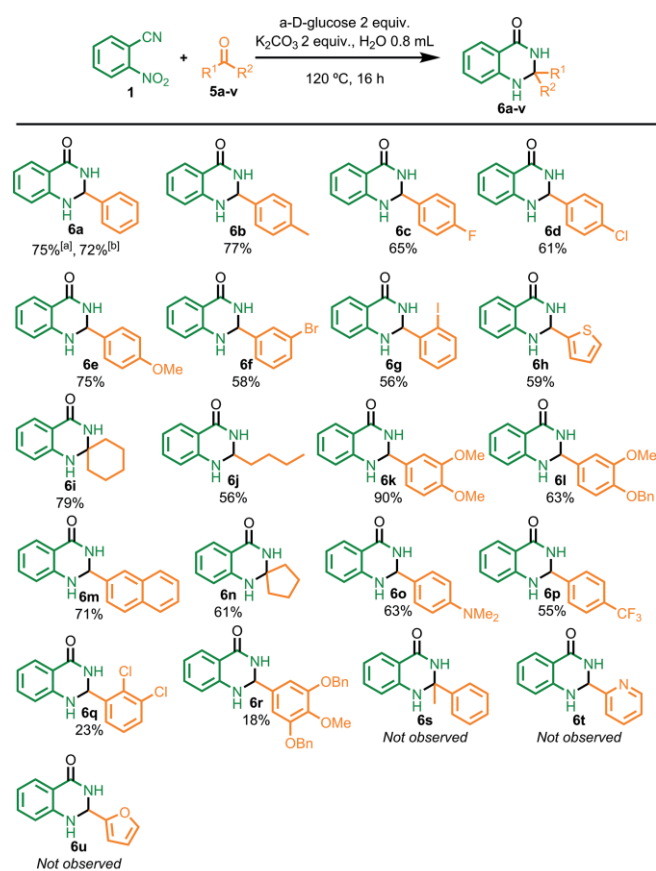
Entry	Solvent (H ₂ O)	Temp. [°C]	Benzaldehyde	Time	Yield [%] ^[b]	2	3	4
1	2 mL	100	1.0 equiv.	16 h	35	**		55
2	2 mL	100	2.0 equiv.	16 h	18	17		54
3	2 mL	120	1.2 equiv.	16 h	13	6		63
4	1 mL	120	1.2 equiv.	16 h	17	(trace)		72
5	1 mL	120	1.5 equiv.	16 h	7	**		75
6	0.8 mL	120	1.5 equiv.	16 h	5	**		78 ^[c]
7	0.6 mL	120	1.5 equiv.	16 h	14	**		72
8	0.8 mL	120	1.5 equiv.	24 h	**	**		76
9 ^[d]	0.8 mL	120	1.5 equiv.	16 h	**	**		77
10 ^[e]	0.8 mL	120	1.5 equiv.	16 h	**	**		74

[a] 0.2 mmol equiv. of 2-nitrobenzonitrile, air as atmosphere, α-D-glucose (2 equiv.), and K₂CO₃ (2 equiv.) were applied for all the reactions unless otherwise stated. [b] Determined by ¹H-NMR using dimethyl sulfone as a standard. [c] Isolated yield: 75 % (white solid). ** Not detected by ¹H-NMR. [d] α-D-Glucose (1.5 equiv.) and K₂CO₃ (3 equiv.) were employed. [e] K₂CO₃ (4 equiv.) was employed.

With the establishment of a one-pot protocol for the synthesis of 2,3-dihydroquinazolin-4(1H)-ones with glucose in alkaline water, the reaction scope was investigated, and the results are summarized in Table 3. Considering electron-rich aldehydes, mono-substituted benzaldehydes bearing electron-donating groups such as methyl and methoxy in *para* position afforded 2,3-dihydroquinazolin-4(1H)-ones in good yields (**6b**, 77 % and

6e, 75 %). Disubstituted benzaldehydes with similar electronic characteristics as for **6k** and **6l** were also tolerated and the former one was produced in the highest isolated yield (90 %). With three substituents as verified in the synthesis of **6r**, the obtained yield was lower. For halogenated benzaldehydes, the yield ranged from low to moderate (23–65 %). Acetophenone did not react with 2-aminobenzamide under the established conditions to furnish **6s** as a limitation. Extending the scope with heterocyclic aldehydes, the product derived from 2-thiophenecarboxaldehyde (**6h**) was isolated in 59 % yield while furfural (**6u**) and 2-pyridinecarboxaldehyde (**6t**) did not produce any noticeable yield. The developed protocol was however suitable for a model aliphatic aldehyde, pentanal, with a moderate yield of 56 % (**6j**) and cyclic aliphatic ketones as for cyclohexanone (**6i**, 79 %) and cyclopentanone (**6n**, 61 %).

Table 3. Substrate scope.^[a]



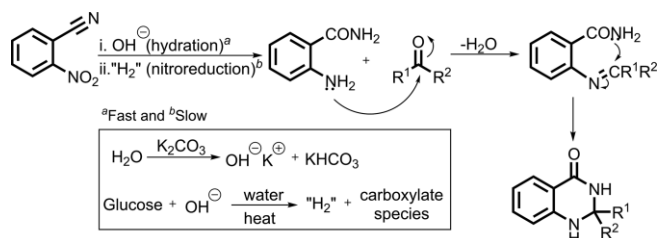
[a] Isolated yields. [b] 0.2 mmol scale. [c] 0.5 mmol scale.

From a mechanistic point of view, it is well established that glucose under hot alkaline conditions produces reduction equivalents ("H₂"), and the hydroxide anion plays an essential role in its decomposition into carboxylates such as formate, lactate, and glycolate.^[11] It was possible to detect formate in the mixture in a standard reaction performed in D₂O (Table 1 – optimized conditions, see the SI). Tu and co-workers have proven the suitability of potassium carbonate to promote the hydration of diverse nitriles and proposed it to deprotonate

water in the generation of this ionic species.^[28] Thus, it is plausible to expect that hydroxide anion can act on glucose decomposition and nitrile hydration at the same time leading to 2-amino-2-benzamide as observed in this study at temperatures equal to or above 100 °C. The facile hydration of 2-nitrobenzonitrile into 2-nitrobenzamide observed at 50 °C profits from the strong electron-withdrawing effect of the *ortho*-nitro group.

The subsequent nitro reduction to the amine may take two different pathways according to the Haber mechanism,^[29] one with a hydroxylamine intermediate and the other one involving heterodimerization to azoxy and azo compounds which are usually formed under high alkaline conditions.^[25,30] However, no azoxy and azo species were observed by Opolonick in the reduction of nitrobenzene to aniline using glucose in water with potassium carbonate.^[31] The synthesis of azoxy compounds can be straightforwardly accomplished by adding glucose to an aqueous solution of NaOH and the nitro compound, while the addition of a second equivalent of glucose reduces the generated azoxy compound to the azo species.^[25,32] To mainly obtain the hydroxylamine while avoiding further reduction to the corresponding amine, glucose can be employed as the reductant in an enzymatic process with a nitroreductase^[33] or in a fermentation with baker's yeast.^[34] Considering the possible competing reactions for the synthesis of 2,3-dihydroquinazolin-4(1H)-ones, it is worth mentioning the amide hydrolysis to the carboxylic acid even with potassium carbonate as verified via HPLC-MS and base-induced reactions^[35] of the aldehyde component.

In summary, the established environmentally friendly one-pot protocol promoting nitrile hydration, nitro-reduction, imine formation and cyclization with glucose in alkaline water (Scheme 2) represents a new, valuable method for the rapid synthesis of 2,3-dihydroquinazolin-4(1H)-ones and can be viewed as a blueprint for the development of further one-pot sequences involving glucose as a reductant. Glucose is an important renewable resource accessible from lignocellulosic biomass through well-established technology while water serves as the solvent and potassium carbonate ("potash", available from plant ashes) as the base. It should be noted that no competition of the aldehyde glucose with the externally added carbonyl compound in the cyclization step was encountered and that aldehyde-derived dihydroquinazolinones can be easily oxidized under eco-friendly conditions^[36] to the corresponding quinazolinones, which find even wider application in medicinal chemistry.^[37]



Scheme 2. Proposed mechanistic pathway for the synthesis of 2,3-dihydroquinazolin-4(1H)-ones from 2-nitrobenzonitrile.

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