One-pot consecutive reductive amination synthesis of pharmaceuticals: from bio-based glycolaldehyde to hydroxychloroquine

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ABSTRACT

Reductive amination plays a paramount role in the synthesis of amines. It is often proposed as a more eco-friendly synthesis process than the traditional S_N2-type reactions of amines as it avoids toxic alkylation reagents such as alkyl halides. This work demonstrates the versatility of the reductive amination reaction via the synthesis of Hydroxychloroquine (HCQ), one of the most renowned pharmaceuticals during this Corona pandemic. The novel green synthesis strategy is based on three consecutive reductive amination reactions conducted in a one-pot system, avoiding intermediary purification steps. Furthermore, a bio-based C_2 platform molecule, glycolaldehyde,

was selected as a starting reagent. The newly developed reductive amination pathway was appraised using the CHEM21 Green Metric Toolkit and compared with the commercially operating method.

INTRODUCTION

At present, it has been widely acknowledged that the chemical industry should evolve toward more environmentally acceptable processes; nevertheless, the introduction of the Green Chemistry concept can already be traced back to the early 1990s.[1] Applying this principle to industrial chemistry requires a paradigm shift from a traditional focus on merely process efficiency that primarily emphasizes chemical yield to one that assigns economic value to reduce waste at source, encourages the utilization of bio-based substrates, and avoids the use and synthesis of toxic and hazardous substances.[2] Since the pharmaceutical industry is considered more of a niche sector within the chemical industry, its influence could be overlooked as, despite the important difference in annual product tonnage, drug manufacturing generates more waste by-products and pollutants than any other chemical industry segment.[3] During active pharmaceutical ingredient (API) manufacturing, approximately 85% of the waste is solvent-related. Thus addressing the selection, use, recovery, and disposal of solvents contributes dramatically to alleviating this waste problem.[3,4] While the higher complexity of the target molecules and the associated multiple synthesis steps combined with the stringent regulatory requirements of drug purity partially justify the substantially elevated waste burden, it also accentuates the opportunity for improvements.[3,5,6]

The amine functional group is widely incorporated in today's commercially available drugs' armory.[7] In this context, reductive amination is commonly proposed as a green way for the synthesis of the amines used as an alternative to the S_N2-type reactions with halides, which helps

avoid stoichiometric amounts of waste.[8] Additionally, due to the impressive advances made in synthesizing bio-derived molecules with reactive functional groups such as aldehydes and ketones, which are often used as precursors in reductive amination, their implementation has sparked much interest over the last few years.[9–11]

In light of the recent SARS-CoV-2 pandemic, much of the ongoing effort is focused on repurposing existing drugs that have undergone extensive testing and were already medically approved. Arguably, Hydroxychloroquine (HCQ), an antimalarial drug and effective medicine in treating rheumatic diseases, was frequently emerged as one of the most renowned yet controversial repurposed drugs.[12,13] However, all recent studies do not support the use of HCQ to treat COVID-19, and most clinical trials are stopped due to insufficient proof of effectiveness. Nevertheless, applying the concept of Green Chemistry to the synthesis of a drug that has been the center of scientific and political obsession epitomizes the possibilities ahead for the pharmaceutical industry.

A typical HCQ synthesis includes a protection–deprotection strategy and is based on a multi-step synthetic process.[14] Although further progress has focused on the retrosynthesis and led to excluding the protection-deprotection step, this synthetic route nearly always comprises one or more traditional S_N2-type substitutions and, therefore, creates stoichiometric amounts of halogenated salt residues. Inspired by Yujiro Hayashi's perspective, we propose in this work a one-pot reaction sequence, minimizing waste and reducing intermediate purifications.[15] Where possible, S_N2-type displacements were substituted by more environmentally benign reductive aminations where several bio-based substrates are implemented. For instance, a bio-based C_2 platform molecule, glycolaldehyde, was selected as a starting reagent. The unique difunctional reactivity has rendered glycolaldehyde much interest in recent years as a sustainable C_2 molecule

that can replace ethylene oxide. Moreover, the safe handling, non-toxicity, and enhanced developments in the bio-based production of this molecule support our choice.[10,16,17]

The greenness of our newly developed reductive amination pathway will be compared to the current synthesis route via the CHEM21 Green Metrics Toolkit, an environmental impact assessment tool developed by Clark *et al*.[18–20] This metric quantitatively calculates the greenness of a reaction and qualitatively indicates the eligibility of the process parameters in terms of solvents, consumed energy, workup, availability by the use of colored flags. While this assessment tool provides a first notion of which synthesis route is considered more eco-friendly, more importantly, the power of the analysis lies in identifying bottle-necks in current methodologies that the greener alternatives might replace.

RESULTS AND DISCUSSION

Inspired by the 12 Principles of Green Chemistry and the CHEM12 consortium, a three-step, one-pot synthesis pathway towards 5-[ethyl(2-hydroxyethyl)amino]pentan-2-one (Scheme 1, intermediate c) is proposed.[18,21,22] This synthesis is based on three consecutively performed reductive amination reactions, carried out with the same catalyst and in the same solvent. Since this work aims to present a proof of concept for possible sustainable improvements in the pharmaceutical industry rather than discuss a complete synthesis, the last step in our proposed synthesis was kept identical to the last step in the commercial synthesis toward HCQ (Figure 1). Moreover, available data suggest that the most significant cost contributor to the commercial synthesis of HCQ is the synthesis of the intermediate molecule 5-[ethyl(2-hydroxyethyl)amino]pentan-2-one and hence advocates why covering part of the total synthesis

suffices.[14] To gain a better understanding, each reaction step will be discussed individually before presenting the complete synthesis (Figure 1).

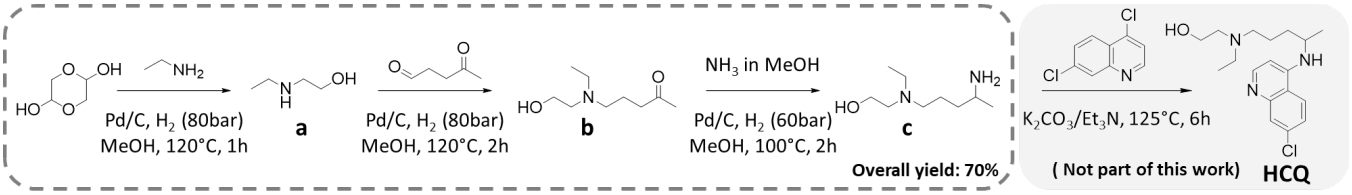


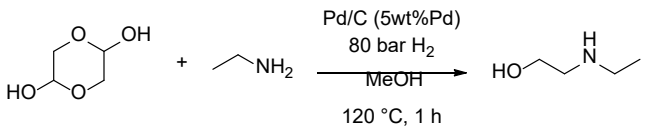
Figure 1 Proposed new catalytic reductive amination pathway for the synthesis of intermediate 5-(*N*-ethyl-*N*-2-hydroxyethylamino)-2-pentylamine (c) in the production of HCQ. a = 2-(ethylamino)ethanol; b = 5-[ethyl(2-hydroxyethyl)amino]pentan-2-one; c = 5-(*N*-ethyl-*N*-2-hydroxyethylamino)-2-pentylamine

Individual step assessment

Step 1: Catalytic reductive amination of glycolaldehyde with ethylamine to 2-(ethylamino)ethanol (a)

Initial evaluations for suitable reaction conditions were commenced by varying the ratio of ethylamine and glycolaldehyde, followed by screening the effect of the H_2 pressure and temperature. The highest yield was obtained when an amine to aldehyde ratio of 2 is used (Table 1, entries 1 – 5). Rather than merely targeting the best yield, in reductive amination reactions, it is of interest to aim at the optimal balance between yield and redundant amine to prohibit its participation in the following reaction steps (Table 1, entry 3). After a further screening of temperature and pressure, a yield of 88% could be reached at a lower temperature (entries 3 and 9), which once more, highlights the potential of glycolaldehyde as an efficient bio-based C_2 platform molecule.

Table 1 Screening of reaction conditions for the catalytic reductive amination of glycolaldehyde (GA) with ethylamine (EtA) [a].



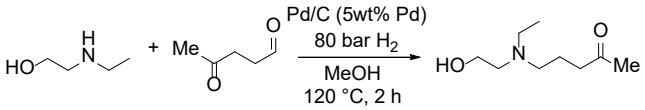
Entry	EtA:GA ratio	Temp. (°C)	H_2 press. (bar)	Yield (%)[b]
1	1:1	120	80	80
2	1.1:1	120	80	89
3	**1.2:1**	**120**	**80**	**90**
4	1.5:1	120	80	92
5	2:1	120	80	94
6	1.2:1	120	20	79
7	1.2:1	120	40	83
8	1.2:1	120	60	87
9	1.2:1	100	80	88
10	1.2:1	140	80	84

[a]Reaction conditions: GA dimer (5 mmol), EtA (mole ratio), Pd/C (1 mol %) and MeOH (V_{tot} = 15ml) for 1h at 800 rpm. [b]Yield was determined by GC-FID with *tert*-amyl alcohol as internal standard at full conversion.

Step 2: Catalytic reductive amination of 2-(ethylamino)ethanol with (a) 4-oxopentanal to 5-[ethyl(2-hydroxyethyl)amino]pentan-2-one (b)

The synthesis of bio-based 4-oxopentanal (scheme 1, reaction 2) was performed as described in the literature.[23] The screening for the optimal reaction conditions for the catalytic reductive amination of 4-oxopentanal by 2-(ethylamino)ethanol was evaluated similarly to step one, and the optimal pressure and temperature of the first step were used as starting points. After optimization of the amine to aldehyde ratio, temperature, and pressure, an optimal yield of 96% could be achieved (entry 4).

Table 2 Screening of reaction conditions for the catalytic reductive amination of 2-(ethylamino)ethanol with 4-oxopentanal [a].



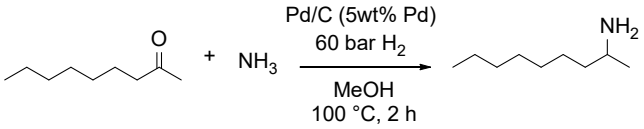
Entry	Amine: aldehyde ratio	Temp. (°C)	H_2 press. (bar)	Yield (%)[b]
1	1:1	100	80	94
2	1.2:1	100	80	91
3	1.3:1	100	80	86
4	**1:1**	**120**	**80**	**96**
5	1:1	140	80	77
6	1:1	120	60	91

[a]Reaction conditions: 4-oxopentanal (1 mmol), 2-(ethylamino)ethanol (mole ratio), Pd/C (1 mol%) and MeOH (V_{tot} = 15ml) for 2h at 800rpm.[b]Yield was determined by GC-FID with *tert*-amyl alcohol as internal standard at full conversion.

Step 3: Reductive amination of 5-[ethyl(2-hydroxyethyl)amino]pentan-2-one (b) with ammonia to 5-(*N*-ethyl-*N*-2-hydroxyethylamino)-2-pentylamine (c)

For the third consecutive reductive amination step, 2-nonanone was used as a model substrate to screen the reaction conditions. Selectively synthesizing primary amines via reductive amination is known to be challenging since they are prone to over-alkylation and hydrogenation of the carbonyl group.[24,25] Indeed, a technique to increase the selectivity to primary amines is to apply an excess of NH_3 (entries 1-4).[26] However, taking the 12 Principles of Green Chemistry into account, which advocate waste prevention by maximizing the incorporation of all materials into the final product, the balance between yield and excess reagent was optimized. Under optimal conditions, a yield of 80% 2-nonanamine was obtained (entry 7).

Table 3 Screening of reaction conditions for the reductive amination of 2-nonanone with ammonia.[a]



Entry	Ammonia: 2-nonanone ratio	Temp. (°C)	H_2 press. (bar)	Yield (%)[b]
1	10:1	100	80	80
2	12:1	100	80	82
3	15:1	100	80	86
4	5:1	100	80	72
5	10:1	120	80	78
6	10:1	140	80	75
7	**10:1**	**100**	**60**	**80**
8	10:1	100	40	68

[a]Reaction conditions: 2-nonanone (4 mmol), 2M ammonia in MeOH (mole ratio), Pd/C (1.0 mol %) and MeOH (Vtot = 30ml) for 2h at 800rpm.[b]Yield was determined by GC-FID with *tert*-amyl alcohol as internal standard at full conversion.

Evaluation of the total reaction pathway

After the optimization of the individual steps, the full reaction was carried out. This was done by consecutively performing the three reductive amination reactions in one-pot. An overall yield of 58% 5-(*N*-ethyl-*N*-2-hydroxyethylamino)-2-pentylamine was obtained (Figure 2). Notably, the overall yield of the consecutive reactions is lower than the overall yield expected after the individual reactions. Most likely the decrease in yield can be attributed to residual reagent amine and formed side-product such as diamine, which stand in direct competition with the substrate during the catalytic reductive amination reaction (Figure S1). Therefore, the consecutive reaction was repeated but with the difference that the first step was performed under sub-optimal reaction conditions. This approach increased the overall yield to 70% 5-(*N*-ethyl-*N*-2-hydroxyethylamino)-2-pentylamine.

Evaluation of the Green Credentials for the synthesis of hydroxychloroquine

Green chemistry has gained momentum over the last 25 years, and several evaluation methods have been proposed. For instance, the E-factor is frequently utilized to assess the relative inefficiency of pharmaceuticals manufacturing as opposed to that of bulk chemicals manufacturing, yet it has also been acknowledged that this comparison has flaws due to varying product complexity.[2,27] Application of the 12 Principles of Green Chemistry can achieve higher efficiency and reduced environmental burden during chemical synthesis, however, not all principles, i.e., designing for degradation, apply directly to the pharmaceutical industry. Therefore,

the CHEM 21 Metric Toolkit was developed to evaluate the sustainability of reactions, encompassing a comprehensive and holistic range of criteria for measuring how green a reaction is.

Different routes toward 5-(*N*-ethyl-*N*-2-hydroxyethylamino)-2-pentylamine have been proposed during the last 50 years. For this analysis, our one-pot consecutive reductive amination pathway is compared to the classical pathway disclosed by Sterling-Winthrop (Figure 2).[28] Over the years, some modifications have been made to this process, including the addition of protection-deprotection steps and the transition from batch to a continuous-flow synthesis, both resulting in an increased product yield.[29,30] Yet, since the CHEM 21 Metric Toolkit does not merely reward high reaction yield but equally punishes increased step economy and waste, the abovementioned pathway, with similar step economy to the catalytic reductive amination pathway, appears to be the fairer comparison. Since 2-(ethylamino)ethanol is produced via ethylene oxide, this was added as to complete the tandem reaction scheme.[31] The result of this assessment tool will provide a first notion on the most suitable reaction pathway. However more importantly, the power of the analysis lies in identifying bottlenecks in current methodologies, which can perhaps be replaced by the more eco-responsible reaction.

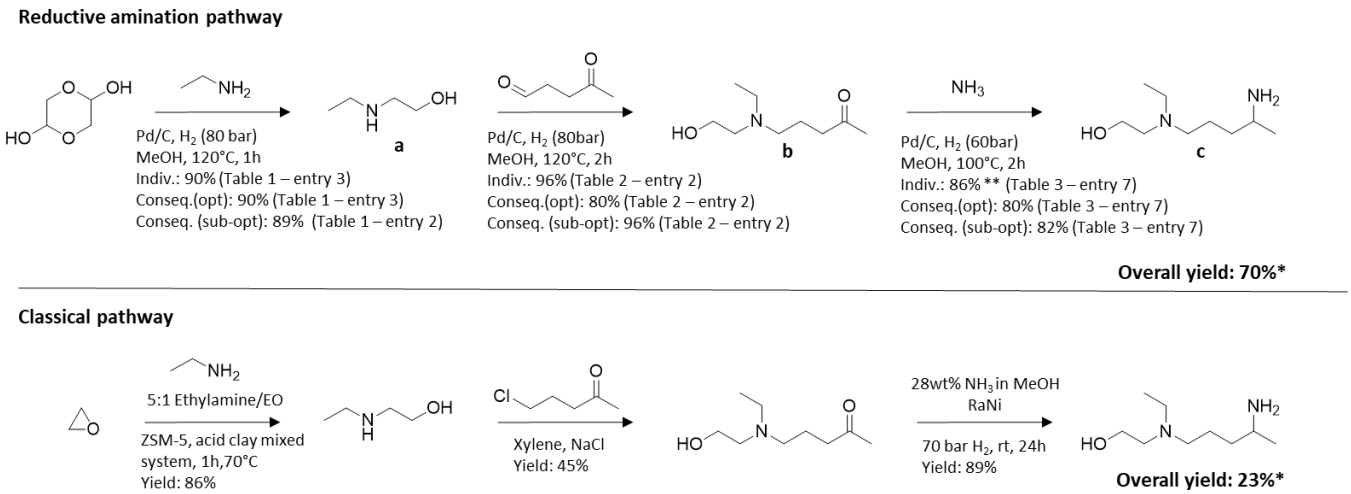


Figure 2 Comparison of the synthesis of intermediate 5-(*N*-ethyl-*N*-2-hydroxyethylamino)-2-pentylamine via the classical pathway and the new proposed catalytic reductive amination pathway. Individual reaction yield and optimal and sub-optimal consecutive reaction yield are reported. (*) Reagent excess is taken into account (SI T5). (**) Reported yield from the catalytic reductive amination of 2-nonanone with ammonia.

The CHEM 21 Metric Toolkit blends quantitative and qualitative criteria to assess the greenness of a reaction, and both criteria will be evaluated. The following cumulative overall values for the quantitative metrics were calculated for both the classical and the reductive amination pathway: Yield, Atom Economy (AE), Reaction Mass Efficiency (RME), Process Mass Intensity (PMI). The latter is the complete mass-based metric and can be calculated for the reactants, reagent, catalyst (PMI RCC), the complete reaction (PMI Rxn), the used amount of solvent (PMI solv) as well as the workup (PMI WU), making it possible to break down the result and add improvements in the procedure where necessary. As can be deduced from table 4 and figure 2, the yield 5-(*N*-ethyl-*N*-2-hydroxyethylamino)-2-pentylamine (intermediate c) obtained via the reductive amination pathway (70%) is substantially higher than the classical pathway (23%). Since the RME is mostly influenced by yield, a similar trend is identified (42 vs. 12%). The step economy and AE are similar for both pathways. In terms of PMI, the classical route (15.7 $g.g^{-1}$) seems to outperform the one-pot consecutive reductive amination pathway (19.2 $g.g^{-1}$). Yet, these values need to be carefully interpreted. It is noteworthy that our reactions are still at the discovery level; hence no optimization has been implemented so far. For instance, the reaction's concentration can be increased by raising the amount of glycolaldehyde, therefore, significantly lowering the PMI solv. A clear advantage of our consecutive reductive amination pathway is that this one-pot synthesis

scores significantly better on the PMI RRC as the same catalyst is used for all three consecutive reactions as on the PMI WU since no intermediate evaporation processes or solvent swapping is involved. Overall, based on these quantitative metrics, it can be stated that the one-pot consecutive reductive amination route is favorable from a green chemistry point of view. Moreover, it is firmly believed that even more distinct results could be obtained regarding the PMI provided that further research increases the concentration and hence the productivity.

Table 4 Calculated cumulative overall quantitative metrics for the synthesis of 5-(*N*-ethyl-*N*-2-hydroxyethylamino)-2-pentylamine via the reductive amination pathway and the classical pathway.

Metric	Yield (%)	AE (%)	RME (%)	PMI ($g\ g^{-1}$)	PMI RRC ($g\ g^{-1}$)	PMI solv ($g\ g^{-1}$)	PMI WU ($g\ g^{-1}$)
1) New synthesis of 5-(*N*-ethyl-*N*-2-hydroxyethylamino)-2-pentylamine	70.3	78.4	35.1	19.2	3.0	16.2	0.0
2) Classical synthesis of 5-(*N*-ethyl-*N*-2-hydroxyethylamino)-2-pentylamine	23.3	76.9	12.1	15.7	8.8	5.3	1.6

In addition to the quantitative mass-based assessment, CHEM21 also focuses on qualitative metrics that indicate the acceptability of the process parameters in terms of solvent, use of catalyst, consumed energy, critical elements, workup, and health and safety (Table 5). Captivating improvement of our one-pot consecutive reductive amination pathway is utilizing a bio-renewable substrate, glycolaldehyde (GA), resulting in a green flag instead of a red one for using ethylene oxide (EO). In addition, "problematic" and "hazardous" solvents were specifically avoided whilst still targeting a suitable solvent for the reaction. Therefore, the reductive amination pathway obtained three green flags for MeOH, whereas the classical method received a yellow (xylene) and a green (MeOH) flag. When assessing the reagents and critical elements used, the classical pathway is penalized in the first two steps for not working catalytically. Furthermore, by designing a synthesis route that consecutively executes the same type of reaction in one-pot, e.g., a reductive

amination, and using a heterogeneous catalyst, the expensive palladium catalyst could efficiently be reused in every step of synthesis and easily recovered after the reaction. From an energy and process perspective, these results indicate that the catalytic reductive amination pathway could further be enhanced by lowering the operating temperature and pressure. Moreover, most pharmaceutical batch processes operate under limited pressure; hence further research on increasing the catalyst activity under lower hydrogen pressure is sensible.

Conclusively, the qualitative metrics demonstrate that the reductive amination pathway is preferred from a solvent, health and safety, and workup perspective. Additional research on the hydrogenation catalyst may further affirm this prospect.

Step	Solvent	Flag	Health and safety	Flag	Catalyst	Flag	Critical element	Flag	Reactor	Flag	Energy	Flag	Workup	Flag
1) Catalytic reductive amination pathway														
1	MeOH		MeOH: H370		Pd/C		Pd		Batch		>70°C		-	
2	MeOH		MeOH: H370		Pd/C		Pd		Batch		>70°C		-	
3	MeOH		MeOH: H370 NH_3: H420		Pd/C		Pd		Batch		>70°C		Filtration + disillation	
2) Classical pathway														
1	-		Ethylene oxide: H230 + H340 + H350		ZSM-5		-	-	Batch		>70°C		-	
2	Xylene				excess reagent		-	-	Batch		>70°C		Fractional disillation	
3	MeOH		MeOH: H370 NH_3: H420		Raney Nickel		Ni		Batch		40°C		Filtration + disillation	

Table 5 Summary of the results from the CHEM21 Green Metrics Toolkit Calculation

CONCLUSION

Over the last few years, catalytic reductive amination has emerged as an environmentally benign and economical route for the synthesis of amines. In this work, the potency of catalytic reductive

amination in the pharmaceutical industry has been demonstrated via the synthesis of an intermediate for hydroxychloroquine (HCQ), arguably one of the most debated drugs in recent years. Compared to the classical pathway, this strategy allowed for a one-pot system which is considerably in line with the 12 Principles of Green Chemistry.

The greenness of the reductive amination pathway was confirmed via the CHEM21 green metrics toolkit and compared to the commercial synthesis route via quantitative and qualitative data. Although the reductive amination pathway is not fully optimized, a yield of 70 % was obtained, contrary to 23% yield via the commercially operating classical pathway. Secondly, performing multiple reaction steps with the same solvent prevented intermediary purification and reduced solvent waste and energy requirements. Analogous, the utilized catalyst was recovered in all three consecutive steps. Moreover, glycolaldehyde, a C_2 platform molecule obtainable from a renewable feedstock, could be utilized as starting reagent and, therefore, significantly contributed to this reaction's greenness. In addition, recent articles report the potential synthesis of 4-oxopentanal from furfural, which can be obtained via the dehydration of carbohydrate-derived pentosans such as xylose. The bio-based prospect of 4-oxopentanal opens new avenues for the catalytic reductive amination and the commercial pathway. Further progress on increasing the reaction concentration is encouraged to improve the Process Mass Intensity (PMI) parameter and additional research on pressure reduction through intelligent catalyst design is desirable to decrease the process energy and meet the reactor requirements of the pharmaceutical industry. Overall, this work clearly shows that, in comparison with the classical S_N2-type displacement pathways, the synthesis of amines via catalytic reductive amination has great potential for the pharmaceutical industry from an environmental and possibly also economic point of view.

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