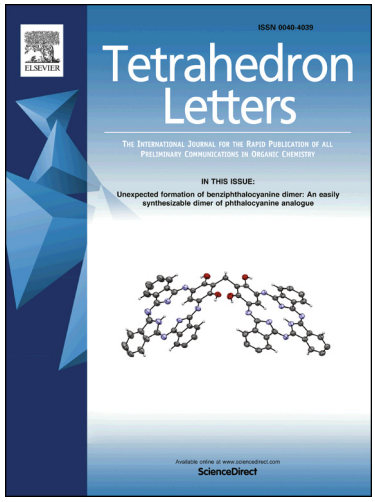

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Preparative-scale synthesis of amino coumarins through new sequential nitration and reduction protocol

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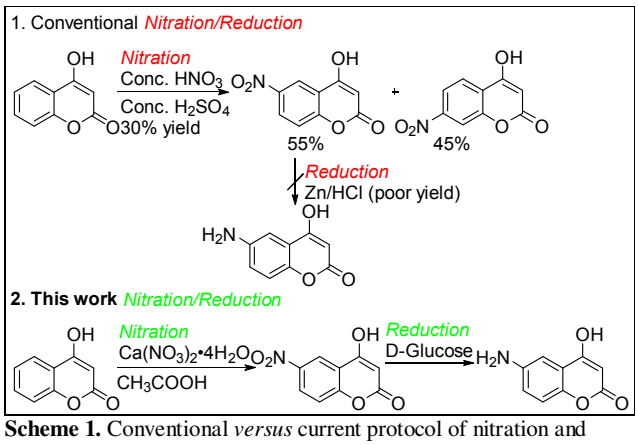
ABSTRACT

In contrast to the conventional deleterious approach for nitration (for example HNO_3/H_2SO_4) and for reduction (for example Zn/HCl), we hypothesized that sensitive heterocycles such as coumarins could not withstand with those hard conditions. Hence, while studying this reaction sequence to prepare amino coumarins (which is our ongoing project to synthesize antitubercular coumarin agents), we came across mild and greener reagent for nitration using calcium nitrate ($Ca(NO_3)_2.4H_2O$; lime nitrate), and reduction using D-glucose. These two mild, chemoselective, high yielding methods are discussed herein.

Nitration and reduction are important reactions in organic synthesis and it is obvious that most common way to do nitration and reduction would be to use cheap commercial available nitrating reagent HNO_3/H_2SO_4 and Zn/HCl, respectively. But how frequently is that possible when it comes to heterocyclic compounds as starting materials? The answer is rare, because these harder conditions would lead to either decomposition of starting materials or other side reactions if applied on heterocycles. At least we have failed to prepare aminocoumarins by using these conventional approaches vide infra (Scheme 1). In this context, chemistry plays a vital role and a variety of mild methods were developed and found in the literature[1, 2]. For example, noteworthy in the case of nitration is the use of acetyl nitrate ($AcONO_2$)[3], triflyl nitrate ($TfONO_2$)[4], $Cr(NO_3)_3.2N_2O_4$[5], $Bi(NO_3)_3$/montmorillonite KSF[6], $NaNO_3$/wet SiO_2[7], PEG-bound metal nitrate[8], $Cu(NO_3)_2$/clay, $Fe(NO_3)_3{\cdot}9H_2O$/ionic liquid[9], and $VO(NO_3)_3$[10]. It should be mentioned here that these methods are although mild and selective, there application on heterocyclic compound is very rare[11]. To test the compatibility and reactivity of coumarin with conventional nitration conditions (HNO_3/H_2SO_4), we reacted hydroxycoumarin with the former and found that poor yield (30%) of mixed regioisomer 6- and 7-nitro coumarin was obtained in the ratio 55:45, respectively. In the other reaction step, which is reduction of nitro group, Zn/HCl is widely used reaction (we could not get good yield), but more convenient and mild methods such as transition metal catalyst along with H_2[12], toxic hydrazine hydrate[13], silanes[14], sodium hydrosulphite[15], formates[16] and decaborane[17] as hydrogen sources have been developed. Additionally, isopropanol or formic acid is used as the hydrogen source for catalytic transfer hydrogenation. However, most of these conditions require tedious work up, toxic and/expensive transition metals which create serious environmental issues[18, 19].



Scheme 1. Conventional *versus* current protocol of nitration and reduction.

In short, the synthesis of aminocoumarines which are very important synthons in pharmaceuticals[20, 21] could not be achieved efficiently using traditional methods in high selectivity and yield. This led us to develop new, mild and efficient method to synthesize biologically important synthons based on aminocoumarins using calcium nitrate and D-glucose for

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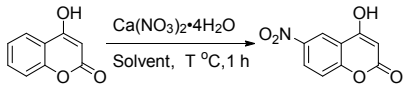
nitration and reduction, respectively. Both Calcium nitrate and D-glucose are relatively greener as well as mild and regioselective reagents, and hence impose a great advantage to be used in organic synthesis[22].

As a starting point, we focused on optimization for nitration of hydroxycoumarin. Accordingly, 6.2 mmol (1.0 g) of **1** was treated with 6.2 mmol of $Ca(NO_3)_2 \cdot 4H_2O$ (1.5 g) in water as solvent at 100 °C, however no expected product was detected (entry 1). Acidic solvent such as H_2SO_4 could not give the desired product (entry 2), instead the decomposition of starting materials was occurred, however use of relatively weak acid like acetic acid was surprising and led to the formation of the desired product in 65% yield (entry 3). While using acetic acid, we found that complete conversion of **1** was obtained but the yield was poor, hence we reduced reaction temperature to 80 °C (entry 4) and 60 °C (entry 5), remarkably we could achieve high chemical yield of the desired product at 60 °C. In fact, lowering the temperature down to 0 °C has negative effect on the reaction and gave very trace amount of the product. Excess use of $Ca(NO_3)_2 \cdot 4H_2O$ did not significantly improve the yield further (entry 6), hence we applied these optimized conditions (entry 5) on other coumarin derivatives and results are summarized in Table 2.

Table 1. Optimization for nitration of hydroxycoumarin (**1a**)[a]



1a **2a**

Entry	Solvent	T (°C)	Yield[b] (%) of **2a**
1	Water	100	No reaction
2	Sulphuric acid	100	No reaction
3	Acetic acid	100	65
4	Acetic acid	80	62
5	**Acetic acid**	**60**	**90**
6	Acetic acid	60	91[c]
7	Acetic anhydride	60	65[d]

[a]Reaction conditions: **1a** (6.2 mmol), $Ca(NO_3)_2 \cdot 4H_2O$ (6.2 mmol), solvent (5 mL) stirred at mentioned temperature for 1 h.

[b]Isolated yield.

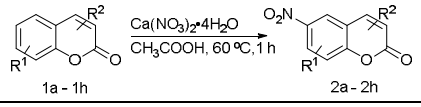
[c]Two equiv. of $Ca(NO_3)_2 \cdot 4H_2O$ was used.

[d]Reaction time was 2 h.

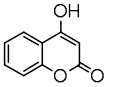
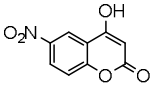
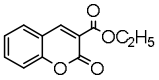
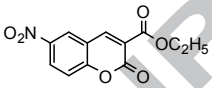
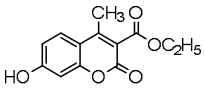
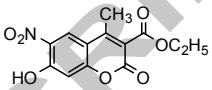
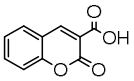
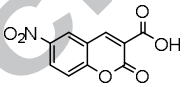
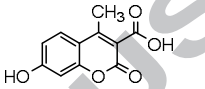
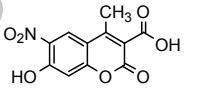
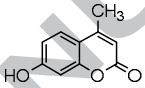
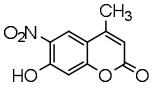
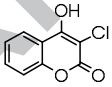
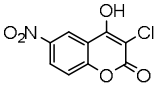
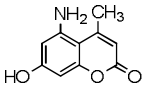
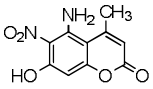
Most of these coumarin derivatives were underwent nitration in high chemical yields (Table 2). Noteworthy to mention is entry 2 and 3 in which ester group was tolerated and no acid catalyzed hydrolysis was observed which would have been difficult to avoid using harsh HNO_3/H_2SO_4 conditions. Also, acid functionality was well tolerated and found to give good chemical yields of the desired products (entry 4 and 5). Chloro group was sufficiently stable in our condition and gave 82% of the desired product (entry 7). One of the interesting examples here is entry 8 where nitration of starting material already bearing basic amine moiety was performed and found to give good yield of the desired product.

It will be early to predict actual mechanism by which coumarin undergo nitration, but it is quite reasonable that $Ca(NO_3)_2$ in the presence of acetic acid led to the formation of some amount of nitric acid and/ CH_3COONO_2 which helps in nitration[23].

Table 2. Nitration of coumarin derivatives using $Ca(NO_3)_2 \cdot 4H_2O$[a]



1a - 1h 2a - 2h

Entry	Reactant **1**	Product **2**	Yield[b](%) of **2**
1			90
2			82
3			90
4			85
5			83
6			89
7			82
8			80

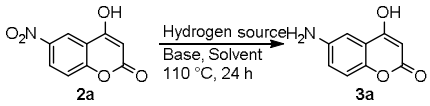
[a]Reaction conditions: **1** (6.2 mmol), $Ca(NO_3)_2 \cdot 4H_2O$ (6.2 mmol), acetic acid (5 mL) stirred at 60 °C for 1 h.

[b]Isolated yield.

After synthesizing nitrocoumarins in high yields using new mild method, we subjected them under newly developed reduction reaction using D-glucose. Although reduction using D-glucose in alkaline media was reported by Galbrait et al.,[24] its wide scope was not studied on heterocycles such as coumarins. Hence it had promoted us to use D-glucose for reduction of coumarins. Initially, 4-hydroxy-6-nitrocoumarin was heated at 120 °C with 1 equivalents of D-glucose and 1 equivalents of KOH in dimethyl sulfoxide (DMSO) as solvent. We could obtain 45% yield of the desired amine in 24 h (entry 1). It seemed to us that recovery of the product from DMSO was not easy hence we tried to input water as additional solvent and found that DMSO: water (1:1) led to slight improvement in the yield (entry 2). Changing the quantity of D-glucose and KOH to 2 equiv and 4 equiv, respectively led to the maximum yield of 65% (entry 3). In fact, we were surprised to see that reaction works well only in water as a solvent (80%, entry 4). Ethanol as a solvent reached chemical yield to 75% (entry 5). Mixed solvent system of ethanol: water (1:9) gave excellent yield of the desired product (entry 6). Changing the reducing source to other carbohydrate such as fructose (entry 7), maltose (entry 8), sucrose (entry 9) did not result in any further improvement in the yield. Use of previously reported transfer hydrogenating quinazoline alkaloid, vascicine was found give satisfactory yield of the desired product but led to difficulty in purifying desired product due to leftover organic impurities from the reducing source (entry 10)[25]. We found that the absence of reducing source but only in the

presence of KOH, reaction failed to give the desired product (entry 11).

Table 3. Reduction of nitrocoumarin derivatives using hydrogen source and base[a]



2a **3a**

Entry	Hydrogen source (equiv)	Base (equiv)	Solvent (ratio)	Yield[b] (%) of **3a**
1	D-glucose (1)	KOH (1)	DMSO	45
2	D-Glucose (1)	KOH (1)	H_2O: DMSO (1:1)	58
3	D-Glucose (2)	KOH (4)	H_2O: DMSO (1:1)	65
4	D-Glucose (2)	KOH (4)	H_2O	80
5	D-Glucose (2)	KOH (4)	EtOH	75
6	D-Glucose (2)	KOH (4)	H_2O: EtOH (9:1)	92
7	Fructose (2)	KOH (4)	H_2O: EtOH (9:1)	40
8	Maltose (2)	KOH (4)	H_2O: EtOH (9:1)	45
9	Sucrose (2)	KOH (4)	H_2O: EtOH (9:1)	no reaction
10[c]	Vasicine	none	H_2O: EtOH (9:1)	80
11	none	KOH (4)	H_2O: EtOH (9:1)	no reaction

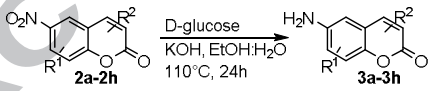
[a]Reaction conditions: Nitrocoumarin (1 mmol), Hydrogen source (2 mmol) Base (4 mmol) and Solvent (4 mL).

[b]Isolated yield.

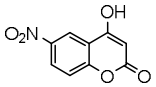
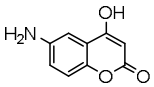
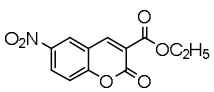
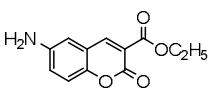
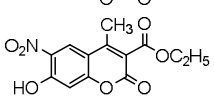
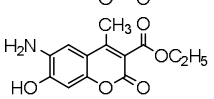
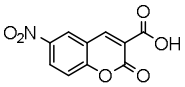
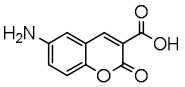
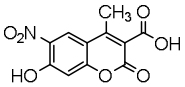
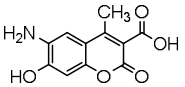
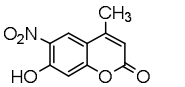
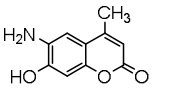
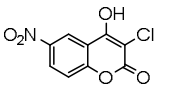
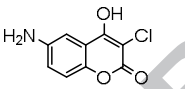
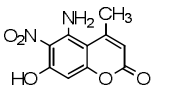
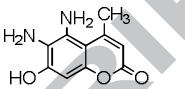
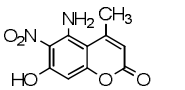
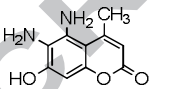
[c]Reduction using literature reported conditions.

With the optimized conditions in hand, we subjected a variety of previously synthesized nitrocoumarins for reduction, and results are summarized in Table 4. Most of the coumarins were reduced in high chemical yield with excellent chemoselectivity (entry 1-8). To prepare the aminocoumarins in gram scale for our subsequent project of coumarin based antitubercular agents, we tested suitability of this protocol for large scale reduction of **2a**, we could obtain satisfactory yield of the desired product **3a** (entry 1, yield in parentheses). Substrates bearing multiple reducible functional groups such as ester derivatives (entry 2 and 3), and acid derivatives (entry 4 and 5) were reduced in excellent chemoselectivity. Sterically demanding substrate such as **2h** could give good yield of the desired product (entry 8). However, this substrate failed to give satisfactory yield of the desired product (entry 9) using conventional reduction strategy (Zn/HCl)

Table 4. Reduction of Nitrocoumarin derivatives using D-glucose[a]



2a-2h **3a-3h**

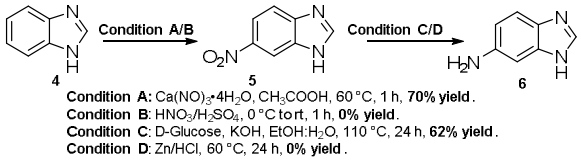
Entry	Reactant **2**	Product **3**	Yield[b] (%) of **3**
1			92 (84)[c]
2			62
3			62
4			62
5			85
6			80
7			80
8			70
9[d]			45

[a]Reaction conditions: Nitrocoumarin **2** (1 mmol), D-glucose (2 equiv), KOH (4 equiv), Solvent (4 mL) stirred at 110 °C.

[b]Isolated yield.

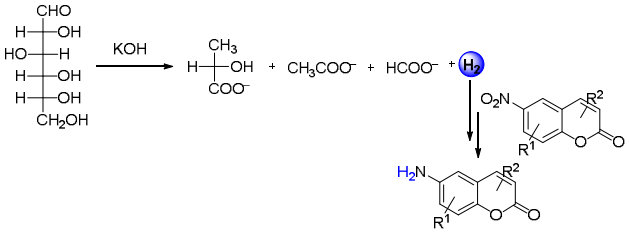
[c]Gram scale (8 mmol) reaction; [d]Reduction was performed using conventional (Zn/HCl) method.

Excited by mild reactivity conditions that $Ca(NO_3)_2{\cdot}4H_2O$ and D-glucose could offer, we were curious to see if these systems have wide applicability. Accordingly, other heterocycle such as benzimidazole **4** was subjected to optimized conditions of nitration/reduction and compared with traditional methods. As expected, acceptable chemical yield of the desired products **5** and **6** was obtained in current optimized condition, while traditional reaction conditions could not give good results.



Scheme 2. Extension of designed nitration/reduction strategy to imidazole.

Our understanding towards the mechanism of reduction is based on the previous facts that D-glucose undergoes degradation in hot alkaline media to produce series of carboxylates along with the hydrogen[23, 26]. We believe that this hydrogen is responsible for reduction of nitrocoumarins (Scheme 3).



Scheme 3. Plausible pathway for reduction using D-glucose.

In conclusion, we have demonstrated a new reaction strategy for high scale synthesis of aminocoumarins which are important synthons in pharmaceuticals. Nitration is achieved using calcium nitrate, while reduction is performed using D-glucose. Both are mild, relatively greener, and cheap, commercially available reagents. There unique selectivity could

prove synthetically useful for nitration and or reduction of various heterocycles.

Acknowledgments

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Preparative-scale synthesis of amino coumarins through new sequential nitration and reduction protocol

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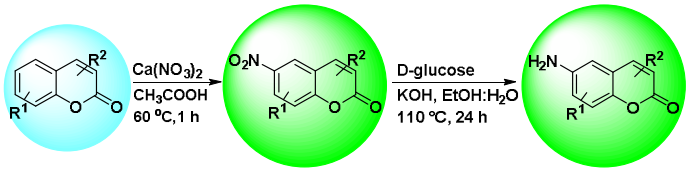
Hemchandra K. Chaudhari[a,*] Akshata Pahelkar[a] and Balaram S. Takale[b]



Highly regioselective # Greener reagents
Preparative scale # High chemical yields

Preparative-scale synthesis of amino coumarins through new sequential nitration and reduction protocol

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A new reaction strategy for high scale synthesis of aminocoumarins which are important synthons in pharmaceuticals. Nitration is achieved using calcium nitrate, while reduction is performed using D-glucose. Both are mild, relatively greener, and cheap, commercially available reagents. There unique selectivity could prove synthetically useful for nitration and or reduction of various heterocycles.