Tetrahedron Letters 58 (2017) 4107–4110

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

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

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

[a] Department of Pharmaceutical Sciences and Technology, Institute of Chemical Technology, Matunga (E), Mumbai 400 019, Maharashtra, India
[b] Department of Chemistry and Biochemistry, University of California, Santa Barbara 93106, USA

ARTICLE INFO

Article history:
Received 31 July 2017
Revised 11 September 2017
Accepted 15 September 2017
Available online 18 September 2017

Keywords:
Amines
Coumarins
Nitration
Pharmaceuticals
Reduction

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 ($Ca(NO_3)_2{\cdot}4H_2O$; lime nitrate), and reduction using D-glucose. These two mild, chemoselective, high yielding methods are discussed herein.

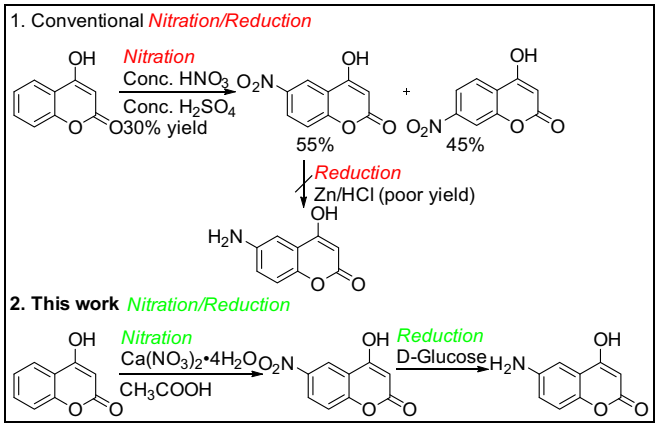
Nitration and reduction are important reactions in organic synthesis and it is obvious that most common way to do nitration and reduction would be to use cheap commercial available nitrating reagent HNO_3/H_2SO_4 and Zn/HCl, respectively. But how frequently is that possible when it comes to heterocyclic 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]

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 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 (Table 1). 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

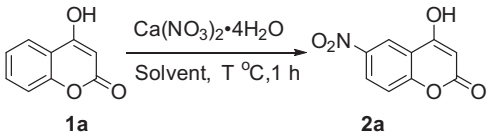
* Corresponding author.
E-mail address: hk.chaudhari@ictmumbai.edu.in (H.K. Chaudhari).

https://doi.org/10.1016/j.tetlet.2017.09.040
0040-4039/



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

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.

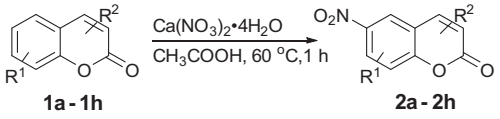
the desired product at 60 °C. In fact, lowering the temperature down to 0 °C has negative effect on the reaction and gave very trace amount of the product. Excess use of $Ca(NO_3)_2{\cdot}4H_2O$ did not significantly improve the yield further (entry 6), hence we applied these optimized conditions (entry 5) on other coumarin derivatives and results are summarized in Table 2.

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.

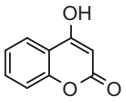
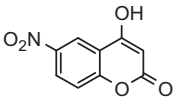
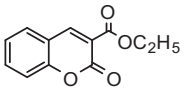
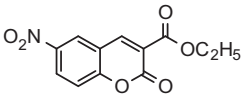
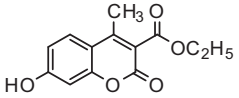
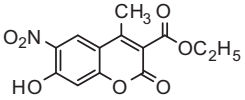
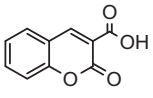
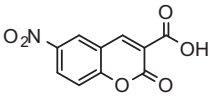
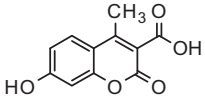
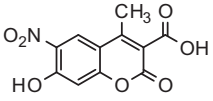
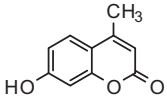
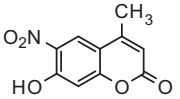
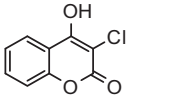
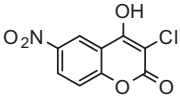
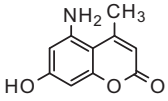
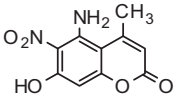
It will be early to predict actual mechanism by which coumarin undergo nitration, but it is quite reasonable that $Ca(NO_3)_2$ in the presence of acetic acid led to the formation of some amount of nitric acid and/CH_3COONO_2 which helps in nitration.[23]

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

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.

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 (Table 3). 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, vasicine was found give