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Title Key: Proline Nitrate: An Efficient Green Organocatalyst____

Proline Nitrate: An Efficient Green Organocatalyst for the Synthesis of Biologically Active Chromeno[2,3-b]quinolin-1-ol

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Abstract

Organocatalyst has been used as a green catalyst for the synthesis of biologically active chromeno[2,3-b]quinoline-1-ol *via* a one-pot multi-component condensation reaction (MCRs) of resorcinol, aromatic aldehydes, malononitrile and cyclohexanone in solvent water at 60 ^{O}C. The environmentally benign, atom economy, simple experimental work-up procedures, metal free conditions, mild reaction conditions and excellent yields of desired products are some of the agreeable features of the method.

Keywords: One-pot synthesis, Organocatalyst, Chromeno[2,3-b]quinoline-1-ol, Resorcinol, Aromatic aldehyde, Malononitrile, Cyclohexanone, etc.

1. Introduction

Chromeno[2,3-b]quinoline-1-ol derivatives exhibit cancer chemopreventive,[1] antibacterial (including anti-tubercular),[2] anti-myopic,[3] hypotensive,[4] anti-rheumatic,[5] and anti-asthmatic activities.[6] During the course of studies on the development of new procedures to synthesize substituted chromeno[2,3-b]quinoline-1-ol, a few procedures have been reported, for instance, two-step synthesis of chromeno[2,3-b]quinoline-1-ol derivatives has been reported by Dushyant et al.[6] 4-[(N-Imidazol-2-ylmethyl)aniline]-chromeno[2,3-b]quinolin-1-ol derivatives were synthesized by Sunkyung et al.[7] However, due to the economical and atom efficiency issues the development of a one-pot, efficient, rapid and convenient protocol for the multicomponent synthesis of chromeno[2,3-b]quinoline-1-ol derivatives are of remarkable interest.

Multi-component condensation reactions (MCRs) are a potent method for the synthesis of organic molecules, since the products are produced in a one step and variety can be achieved by simply varying each component.[8] Due to their simple operations and good results, MCRs have attracted much attention.[9,10]

Due to our attention in organocatalyzed synthesis[11-13] herein we report successful method for synthesis of chromeno[2,3-b]quinoline-1-ol derivatives in excellent yields using proline nitrate as a organocatalyst (**Scheme 1**).

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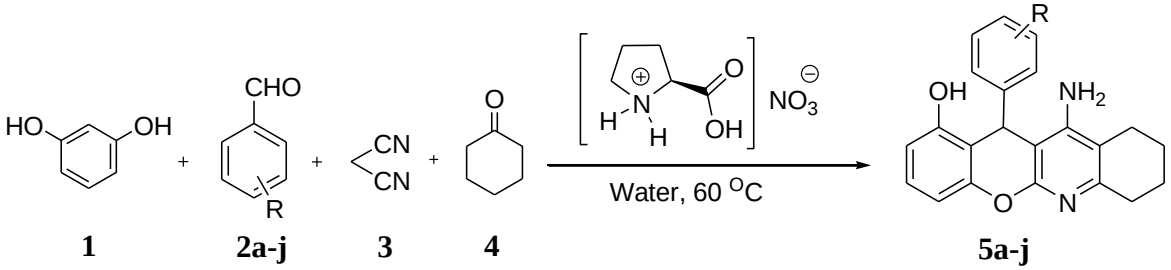

1 **2a-j** **3** **4** **5a-j**

Scheme 1

2. Experimental

All solvents were used as commercial anhydrous grade without further purification. Melting points were determined in open capillary tube and are uncorrected. The IR spectra were recorded on Varian FTIR 640 spectrometer. ^{1}H spectra were recorded on a Bruker 100 MHz spectrometer in $CDCl_3$ solvent and TMS as an internal standard. ^{13}C NMR spectra were recorded on a Bruker-100 MHz spectrometer in $CDCl_3$ solvent. Mass spectra were taken on Polaris-Q Thermoscintific GC-MS.

General procedure for synthesis of 11-amino-8,9,10,12-tetrahydro-12-phenyl-7H-chromeno[2,3-b]quinolin-1-ol derivatives: Resorcinol (1 mmol), malononitrile (1.1 mmol), aromatic aldehyde (1 mmol), cyclohexanone (1 mmol)were added to a 50 mL round bottom flask containing Proline nitrate organocatalyst (15 mol %) in solvent water. The mixture was then stirred at 60 ^{o}C for appropriate time (monitored by TLC) as indicated in table 2. After completion of the reaction, reaction mixture were poured on the crushed ice and filtered re-crystallized from alcohol.

11-amino-12-(4-bromophenyl)-8,9,10,12-tetrahydro-7H-chromeno[2,3-b]quinolin-1-ol (4k): mp: 278–279 ^{O}C. IR (KBr): 3434, 3376, 2977, 1607, 1488, 1206, 1167 cm^{-1}. ^{1}H NMR (100 MHz, DMSO-d_6): δ = 1.64 (m, 4H, CH_2), 2.28 (m, 2H, CH_2), 2.55 (m, 2H, CH_2), 5.40 (s, 1H, CH), 6.35 (br, 2H, NH_2), 6.65–7.40 (m, 7H, ArH), 9.80 (s, 1H, OH). Anal. Calcd for $C_{22}H_{19}BrN_2O_2$: C, 62.42; H, 4.52; N, 6.62. Found: C, 62.17; H, 4.44; N, 6.73.

11-amino-8,9,10,12-tetrahydro-12-(4-methoxyphenyl)-7H-chromeno[2,3-b]quinolin-1-ol (4c): mp: 293–295 ^{O}C. IR (KBr): 3475, 3388, 2907, 1619, 1455, 1223, 1166 cm^{-1}. ^{1}H NMR (100 MHz, DMSO-d_6): δ = 1.55 (m, 4H, CH_2), 2.25 (m, 2H, CH_2), 2.40 (m, 2H, CH_2), 3.75 (s, 3H, OCH_3), 5.55 (s, 1H, CH), 6.25 (s, 2H, NH_2), 6.6–7.4 (m, 7H, ArH), 9.75 (s, 1H, OH). Anal. Calcd. for $C_{23}H_{22}N_2O_3$: C, 73.78; H, 5.92; N, 7.48. Found: C, 73.52; H, 5.80; N, 7.34.

11-amino-8,9,10,12-tetrahydro-12-p-tolyl-7H-chromeno[2,3-b]quinolin-1-ol (4l): mp: 285–286. IR (KBr): 3455, 3365, 2910, 1613, 1433, 1218, 1165 cm^{-1}. ^{1}H NMR (100 MHz, DMSO-d_6): δ = 1.60 (m, 4H, CH_2), 2.20 (s, 3H, CH_3), 2.35 (m, 2H, CH_2), 2.55 (m, 2H, CH_2), 5.40 (s, 1H, CH), 6.10 (s, 2H, NH_2), 6.45–7.20 (m, 7H, ArH), 9.63 (s, 1H, OH). Anal. Calcd for $C_{23}H_{22}N_2O_2$: C, 77.07; H, 6.19; N, 7.82. Found: C, 76.73; H, 6.30; N, 7.71.

11-amino-8,9,10,12-tetrahydro-12-phenyl-7H-chromeno[2,3-b]quinolin-1-ol (4f): mp: 310–311 ^{O}C. IR (KBr): 3440, 3365, 3018, 1614, 1527, 1238, 1111 cm^{-1}. ^{1}H NMR (100 MHz, DMSO-d_6): δ = 1.60 (m, 4H, CH_2), 2.30 (m, 2H, CH_2), 2.62 (m, 2H, CH_2), 5.33 (s, 1H, CH), 6.75–7.45 (m, 10H, ArH, NH_2), 9.60 (s, 1H, OH). Anal. Calcd for $C_{22}H_{20}N_2O_2$: C, 76.72; H, 5.85; N, 8.13. Found: C, 75.66; H, 5.99; N, 7.95.

3. Results and Discussion

In continuation of our interest in synthesis of heterocycles[14,15], herein we describe the synthesis of 11-amino-8,9,10,12-tetrahydro-12-phenyl-7H-chromeno[2,3-b]quinolin-1-ol derivatives in presence of catalytic amount of proline nitrate as a organocatalyst. The synthesis of 11-amino-8,9,10,12-tetrahydro-12-phenyl-7H-chromeno[2,3-b]quinolin-1-ol derivatives was accomplished by a one-pot four-component reaction of resorcinol, aromatic aldehydes, malononitrile and cyclohexanone in solvent water at 60 ^{O}C. Initially, we focused on optimization of suitable solvent and catalyst loading for the model reaction of resorcinol, 4-chlorobenzaldehyde, malononitrile and cyclohexanone.

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Various solvents were screened to test the efficiency of organocatalyst (10 mol%), as shown in table **1**, it is noteworthy to reveal that the agreeable result was observed in the solvent water. Furthermore the reaction in solvents ethanol and methanol afforded 60 % and 52% yield respectively. In the non-polar solvent chloroform and dichloromethane desired product was obtained in lower yields. Therefore we continued our studies in the solvent water.

Afterward, we studied the effect of catalyst loading on the model reaction. It was examined that amount of the catalyst plays a major role in determining the desired product yield. On decreasing catalyst concentration to 5 mol%, reaction offered lower yield 65% with elongated reaction time. When catalyst loading was enhanced to 15 mol%, an improved result was obtained. The reaction was completed within 25 minutes and afforded 93% yield of the desired product. Therefore, the finest optimized reaction condition was accomplished at the catalyst loading of proline nitrate as a organocatalyst to 15 mol% in water. More increase in the catalyst loading to 20 mol% did not show an enhancement in the product yield or reaction time. The model reaction in absence of catalyst in solvent water showed abridged performance with respect to the yield and reaction time.

Table 1: Optimization of the solvent and catalyst concentration for the synthesis of chromeno[2,3-b]quinoline-1-ol derivatives[a]

Entry	Proline nitrate (mol %)	Solvent	Time (min)	Yield[b] (%)
1	10	Ethanol	60	60
2	10	Methanol	80	52
3	10	Water	45	74
4	10	Chloroform	120	45
5	10	DCM	110	48
6	5	Water	55	65
7	**15**	**Water**	**25**	**93**
8	20	Water	30	84
9	-	Water	120	54

[a]Conditions: Resorcinol (1 mmol), 4-Chloro benzaldehyde (1 mmol), malononitrile (1.1 mmol), cyclohexanone (1 mmol), proline nitrate as a organocatalyst (mol %), Solvent (10 mL) at 60 ^{O}C. Reaction was monitored by thin layer-chromatography. [b]Isolated yield.

Table 2: Proline nitrate organocatalyzed one-pot synthesis of chromeno[2,3-b]quinoline-1-ol derivatives[a].

Entry	R	Products	Time (min)	Mp. (^{O}C)	Yield (%)[b]
1	4-OH	**5a**	30	315-316	86
2	4-F	**5b**	25	305-307	85
3	4-OCH_3	**5c**	30	293–295	92
4	3,4,5-OCH_3	**5d**	35	320-321	88
5	3,4-OCH_3	**5e**	30	315-316	90
6	-H	**5f**	30	310-311	83
7	4-Cl	**5g**	25	322-324	93
8	3-OCH_3,4-OH	**5h**	35	295-297	91
9	2-OH	**5i**	30	299-300	89
10	3-NO_2	**5j**	25	290-292	85
11	4-Br	**5k**	30	302-303	87
12	4-CH_3	**5l**	35	285-286	91

[a]Conditions: Resorcinol (1 mmol), 4-Chloro benzaldehyde (1 mmol), malononitrile (1.1 mmol), cyclohexanone (1 mmol), proline nitrate as a organocatalyst (mol %), Solvent (10 mL) at 60 ^{O}C. Reaction was monitored by thin layer-chromatography. [b]Isolated yield.

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To study the scope of the reaction after the optimization of reaction condition, we have examined a wide range of aromatic aldehydes with resorcinol, malononitrile and cyclohexanone to obtain the corresponding 11-amino-8,9,10,12-tetrahydro-12-phenyl-7H-chromeno[2,3-b]quinolin-1-ol derivatives in excellent yields (Table 2, entry 1-12). The reaction proceeded smoothly with aromatic aldehyde having electron-withdrawing or electron-releasing substituents.

4. Conclusion

In conclusion, we have developed a convenient one-pot multi-component protocol for the synthesis of 11-amino-8,9,10,12-tetrahydro-12-phenyl-7H-chromeno[2,3-b]quinolin-1-ol derivatives by the condensation of resorcinol, aromatic aldehydes, malononitrile and cyclohexanone in solvent water at 60 ^{O}C. The remarkable features of this protocol are use of environmentally benign reaction solvents and catalyst, easy to accomplish, mild reaction condition, metal-free conditions and excellent yields of 11-amino-8,9,10,12-tetrahydro-12-phenyl-7H-chromeno[2,3-b]quinolin-1-ol derivatives.

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