



A Novel Catalyst for One-pot Synthesis of Tetrahydrobenzo[b]pyran derivatives

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ABSTRACT

We report herein the use of Nickel nitrate hexahydrate ($Ni(NO_3)_2 \cdot 6H_2O$) as a new catalyst for the one-pot Biginelli-like reaction coupling of dimedone, malononitrile and aromatic aldehydes to afford the corresponding Benzo-[b]-pyran derivatives in aqueous media to avoid the usage of hazardous organic solvents. The experimental conditions have been thoroughly optimized and established, allowing significant rate enhancements and excellent yields.

Keywords: Biginelli-like reaction, aqueous media, Lewis acid, Nickel nitrate hexahydrate, Tetrahydrobenzo[b]pyran.

INTRODUCTION

Benzopyrans and their derivatives have shown several biological and pharmacological properties such as anticoagulant, spasmolytic, diuretic, anticancer and antianaphylactin characteristics [1-6]. Furthermore, they are widely used in cosmetics, pigments and utilized as potential biodegradable agrochemicals [7]; consequently, these compounds have attracted current interest in the organic and medicinal chemistry which can be readily realized from the appearance of huge number of articles dealing with their synthesis and their useful biological and pharmacological properties [8,9].

It is noteworthy that the catalyst is the reagent on which depends the efficiency of any procedure because, not only, it intrinsically minimizes the production of waste material, helps reduce pollution, cuts costs of production etc., that are important principles of Green Chemistry, but also, it decreases activation energy of a reaction which results in milder reaction conditions. As a result, all the strategies revealed by literature survey are dealing with the development of novel catalytic materials [10-26], therefore, the purpose of the present article was focused on the determination of a novel, an inexpensive, convenient available, recovered and high yielding catalyst towards the synthesis of this important class of compounds *via* one-pot three-component Biginelli-like reaction.

EXPERIMENTAL SECTION

All products were characterized by mp, IR and 1H NMR. Melting points were measured using a fine control Electro thermal capillary apparatus and are uncorrected. 1H NMR spectra were recorded on a BRUKER AVANCE DPX spectrometer at 250 MHz. NMR spectra were obtained on solutions in $DMSO-d_6$. Chemical shifts are reported in parts of million (δ , ppm) relative to TMS (δ , 0.0) as internal standard and coupling constant (J) is reported in hertz (Hz). IR spectra were obtained as potassium bromide (KBr) pellets with a Shimadzu FT IR-8201 PC spectrometer. Thin layer chromatography (TLC) on commercial aluminum-backed plates of silica gel, 60 F254, was used to monitor the progress of reactions.

General procedure for the synthesis of tetrahydrobenzo[b]pyran derivatives (4a-h)

A mixture of an appropriate aldehyde (1 mmol), malononitrile (1 mmol) and dimedone (1 mmol), in the presence of $Ni(NO_3)_2 \cdot 6H_2O$ (10 mol%) in water (5 ml) was refluxed within 20 min; after completion of the reaction as indicated

by TLC, the reaction mixture was poured into ice water and filtered. The residue was purified by recrystallization from EtOH to yield the corresponding tetrahydrobenzo[b]pyran. The aqueous layer was evaporated, under reduced pressure, and the catalyst was recovered.

Physical and spectral data for all the compounds

2-Amino-3-cyano-7,7-dimethyl-4-(phenyl)-5-oxo-4H-5,6,7,8-tetrahydro-benzo[b]pyran (4a) IR (KBr) ν_{\max} = 3394(NH₂), 3325 (NH₂), 2199 (C≡N), 1676 (C=O), 1215 (C–O). ¹H NMR (250 MHz, DMSO-d₆): δ = 7.27–7.18 (m, 5H), 6.98 (s, 2H), 4.17 (s, 1H), 2.51 (s, 2H), 2.25 (d, *J*=16.1 Hz, 1H), 2.10 (d, *J*=16.1 Hz, 1H), 1.04 (s, 3H), 0.96(s, 3H);

2-Amino-4-(4-Chlorophenyl)-3-cyano-7,7-dimethyl-5-oxo-4H-5,6,7,8-tetrahydro- benzo[b]pyran (4b)

IR (KBr) : ν_{\max} = 3379 (NH₂), 3322 (NH₂), 2190 (C≡N), 1679 (C=O), 1215 (C–O); ¹H NMR (250 MHz, DMSO-d₆): δ = 7.34 (d, *J* ¼ =8.4 Hz, 2H), 7.17 (d, *J* ¼ =8.4 Hz, 2H), 7.04 (s, 2H), 4.19 (s, 1H), 2.50 (s, 2H), 2.24(d, *J*=16.1 Hz, 1H), 2.10 (d, *J*=16.1 Hz, 1H), 1.03 (s, 3H), 0.94 (s, 3H).

2-Amino-7,7-dimethyl-4-(4-hydroxyphenyl)-5-oxo-5,6,7,8- tetrahydro-benzo[b]pyran (4c) IR (KBr): ν_{\max} = 3452 (NH₂), 3414 (NH₂), 2199 (C≡N), 1651 (C=O), 1215 (C–O). ¹H NMR (250 MHz, DMSO-d₆): δ = 9.30 (s, 1H),6.96–6.89 (m, 4H), 6.67 (d, *J*=8.4 Hz, 2H), 4.07 (s, 1H), 2.55–2.43 (m,2H), 2.24 (d, *J*=16.1 Hz, 1H), 2.09 (d, *J*=16.1 Hz, 1H), 1.03 (s, 3H), 0.95(s, 3H).

2-Amino-7,7-dimethyl-4-(3-nitrophenyl)-5-oxo-5,6,7,8-tetrahydro-benzo[b]pyran (4d)

IR (KBr): ν_{\max} = 3436 (NH₂), 3333 (NH₂), 2187(C≡N), 1674 (C=O), 1213 (C–O); ¹H NMR (250 MHz, DMSO-d₆): δ = 8.06–8.04(m, 2H), 7.65–7.62 (m, 1H), 7.52–7.48 (m, 1H), 6.30 (s, 2H), 4.47 (s,1H), 2.52 (s, 2H), 2.26 (d, *J*= 16 Hz, 1H), 2.15 (d, *J*= 16 Hz, 1H),1.11 (s, 3H), 1.07 (s, 3H).

2-Amino -7,7-dimethyl-4-(4-nitrophenyl)-5-oxo-5,6,7,8-tetrahydro-benzo[b]pyran (4e)

M.p. IR (KBr): ν_{\max} = 3392 (NH₂), 3322 (NH₂), 2190 (C≡N), 1684 (C=O), 1215 (C–O). ¹H NMR (250 MHz, DMSO-d₆): δ = 8.17 (d, *J*=8.72 Hz, 2H), 7.44 (d, *J* =8.72 Hz, 2H), 7.07(s, 2H), 4.36 (s, 1H), 2.50 (s, 2H), 2.26 (d, *J*=15.7 Hz, 1H), 2.11 (d, *J*=15.7 Hz,1H), 1.04 (s, 3H), 0.96 (s, 3H).

2-Amino-4-(4-methoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-benzo[b]pyran (4f)

IR (KBr): ν_{\max} = 3375 (NH₂), 3352 (NH₂), 2193(C≡N), 1684 (C=O), 1214 (C–O). ¹H NMR (250 MHz, DMSO-d₆): δ = 7.05 (d, *J*=8.1 Hz,2H), 6.94 (s, 2H), 6.84 (d, *J*=8.1 Hz, 2H), 4.12 (s, 1H), 3.71 (s, 1H), 2.50(s, 2H), 2.24 (d, *J*=16.1 Hz, 1H), 2.09 (d, *J*=16.1 Hz, 1H), 1.03 (s, 3H), 0.94 (s, 3H);

2-Amino-4-(4-methylphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-benzo[b]pyran (4g)

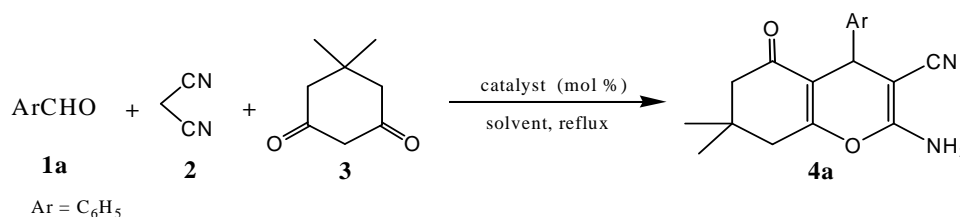
IR (KBr): ν_{\max} = 3395 (NH₂), 3330 (NH₂), 2195 (C≡N), 1675 (C=O), 1213 (C–O). ¹H NMR (250 MHz, DMSO-d₆): δ = 7.11–7.05 (m, 4H), 5.60 (s, 2H), 4.33 (s, 1H), 2.44 (s, 2H), 2.28(s, 3H), 2.195 (d, *J*=16.1 Hz, 1H), 2.16 (d, *J*=16.1 Hz, 1H), 1.11 (s,3H), 1.01 (s, 3H).

2-Amino-4-(furan-2-yl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-benzo[b]pyran (4h)

IR (KBr): ν_{\max} = 3398(NH₂), 3329(NH₂), 2197(C≡N), 1681(C=O), 1218(C–O). ¹H NMR (250 MHz, DMSO-d₆): δ = 7.43 (s, 1H), 7.07 (s, 2H), 6.34 (s, 1H), 6.08 (d, *J*=2.2 Hz, 1H), 4.33 (s,1H), 2.48 (q, *J*=17.9 Hz, 2H), 2.28 (d, *J*=16.1 Hz, 1H), 2.16 (d, *J*=16.1 Hz, 1H), 1.04 (s, 3H), 0.98 (s, 3H).

RESULTS AND DISCUSSION

In order to develop a viable reaction conditions, a variety of Lewis acid catalysts were first investigated for the model multicomponent reaction of benzaldehyde **1a**, malononitrile **2** and dimedone **3** under refluxing ethanol (Scheme-1). The outcome is given in Table 1 (entries 1-5).



Scheme 1

Table 1. Conditions optimization in the synthesis 2-Amino-3-cyano-7,7-dimethyl-4-(phenyl)-5-oxo-4H-5,6,7,8-tetrahydro-benzopyran 4a.

Entry	Catalyst (mol %)	Solvent	Yield ^a (%)
1	none	EtOH	57
2	Ni(NO ₃) ₂ .6H ₂ O (10 mol%)	EtOH	95
3	Pb(NO ₃) ₂ (10 mol%)	EtOH	81
4	SnCl ₂ (10 mol%)	EtOH	73
5	AlCl ₃ (10 mol%)	EtOH	69
6	Ni(NO ₃) ₂ .6H ₂ O(5 mol%)	EtOH	85
7	Ni(NO ₃) ₂ .6H ₂ O(10 mol%)	EtOH	95
8	Ni(NO ₃) ₂ .6H ₂ O(15 mol%)	EtOH	75
9	Ni(NO ₃) ₂ .6H ₂ O(20 mol%)	EtOH	73
10	Ni(NO ₃) ₂ .6H ₂ O(10mol%)	EtOH	95
11	Ni(NO ₃) ₂ .6H ₂ O(10mol%)	CH ₃ CN	73
12	Ni(NO ₃) ₂ .6H ₂ O (10mol%)	THF	90
13	Ni(NO ₃) ₂ .6H ₂ O (10mol%)	H ₂ O	91

^a Reaction conditions: benzaldehyde (1 mmol), malononitrile (1mmol), dimedone (1 mmol), solvent (5 ml), reflux, 20 min.

The data reveals that in the absence of the catalyst, the reaction afforded 2-amino-3-cyano-7,7-dimethyl-4-(phenyl)-5-oxo-4H-5,6,7,8-tetrahydro-benzopyran **4a** in only 57% yield (Table 1, entry 1). The use of AlCl₃ promoted the reaction to a reasonable extent (69%, Table 1, entry 5), but the other catalysts such as SnCl₂, Pb(NO₃)₂ gave better yields (Table 1, entries 2 and 3). It is interesting to note that the above mentioned reaction in the presence of Ni(NO₃)₂.6H₂O gave rise to 95% yield of the product **4a** in 20 minutes, the conversion was found to be the optimum; a further stirring of the reaction mixture for prolonged time gave no substantial increase in the yield. Then efforts have been taken for optimization of the catalytic amount of Ni(NO₃)₂.6H₂O and it was found that 10 mol% was required as a catalyst for the present transformation (entries 6-9, Table 1). Furthermore, different solvents were examined by using the model reaction in the presence of Ni(NO₃)₂.6H₂O (10 mol %) as catalyst (entries 10-13). As shown in table 1, the reaction in EtOH, within 20 min at reflux temperature, gave the corresponding benzo-pyran **4a** in 95% yield (Table 1, entry 10). Both THF and H₂O proved to be good (90% yield in THF, 91% yield in H₂O) (Table 1, entries 12 and 13), while in CH₃CN, the yield was only 73% (Table 1, Entry 11). Due to environmental safety reasons, we chose H₂O as the best solvent.

Having established the reaction conditions, various aromatic aldehydes **1a-h** were allowed to undergo multicomponent reaction with malononitrile **2** and 5,5-dimethyl-cyclohexane-1,3-dione **3** in a molar ratio of 1:1:1 in the presence of Ni(NO₃)₂.6H₂O (10 mol%) in water to afford a range of substituted tetrahydrobenzo[b]pyrans **4a-h** in good yields. The results were listed in Table-2.

Table 2: Synthesis of tetrahydrobenzo[b]pyran 4a-h.

Compd. ^a	Ar	Yield ^b (%)	M.P (°C) ^c	
			Found	reported
4a	C ₆ H ₅	95	233–235	233–234 [27]
4b	4-ClC ₆ H ₄	88	215–218	215–218 [27]
4c	4-OHC ₆ H ₄	97	214–216	214–215 [29]
4d	3-NO ₂ C ₆ H ₄	90	201–205	201–205 [28]
4e	4-NO ₂ C ₆ H ₄	86	175–176	175–176 [28]
4f	4-OCH ₃ C ₆ H ₄	90	199–201	197–199 [28]
4g	4-CH ₃ C ₆ H ₄	97	209–211	209–211 [28]
4h	2-furfural	98	216–217	218–220 [30]

^a Compounds were characterized by their spectral data (IR and ¹H NMR).

^b Yields refer to pure isolated products.

^c M.p are in full agreement with literature.

Aromatic aldehydes with substituents carrying either electron-donating or electron-withdrawing groups reacted successfully and gave the products in high yields. To demonstrate the scope of the procedure, the reaction of the heteroaromatic aldehyde viz. furane-2-carbaldehyde was studied, and the results are summarized in Table 2. Moreover, in all cases, tetrahydrobenzo[b]pyran was the only product and no byproduct was observed. To show the

advantage of this work, various catalysts in synthesis of 2-amino-4-benzopyran derivatives have been compared. The results with respect to the reaction time and yields of the products are listed in Table 3.

Table-3: Comparison results of Nickel nitrate with other catalysts reported in the literature

Entry	Catalyst	Catalyst conditions	Time	Yield (%)
1	Ni(NO ₃) ₂ .6H ₂ O	H ₂ O	20 min	88-98[this work]
2	HDMBAB	H ₂ O	7-8h	84-93[11]
3	TMAH	H ₂ O	0.5-2h	79-93 [22]
4	TBAF	H ₂ O	0.5-5h	73-98[21]
5	Na ₂ SeO ₄	EtOH/H ₂ O	0.75-3h	80-98[19]
6	TBABr	H ₂ O	1-11.25h	85-91 [12]

As shown in Table-5, our catalyst gives a comparative yield and costs less time than others (entry 1, table 3).

CONCLUSION

In conclusion, nickel nitrate hexahydrate can serve as an efficient catalyst for the synthesis of tetrahydrobenzo[b]pyran in aqueous media. This procedure offers several advantages including mild reaction conditions, high yields of products as well as a simple experimental and work-up procedure which makes it a useful and attractive process for the synthesis of these compounds.

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