An Efficient, Simple and Green Zn(Phen)$_2$Cl$_2$
Complex Catalyzed Synthesis of 4-H-Benzo[b]pyrans
in Water at Ambient Temperature

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Received 16 June 2010; Accepted 1 September 2010

Abstract: An efficient method for the synthesis of 4-H-benzo[b]pyrans has been
developed by the use of Zn(Phen)$_2$Cl$_2$ (2 mol%) as an ecofriendly catalyst. The
mixture of an appropriate aldehyde, malononitrile and dimedone in the presence
of the Zn(Phen)$_2$Cl$_2$ as an inorganic catalyst in water at room temperature resulted
excellent yields of the corresponding products in 5 min. Very short experimental
time of the reaction, excellent yields, use of water as a green solvent, simple
work-up and uses no extra catalyst and purification are the advantages of this
method.

Keywords: Zn(Phen)$_2$Cl$_2$, 4-H-Benz[O][b]pyrans, Malononitrile, Transition metal, Green chemistry.

Introduction

4-H-Benzo[b]pyrans and their derivatives are of considerable interest due to their
pharmacological activities$^1$, such as spasmylytic, diuretic, anti coagulant, anti-cancer,
anti-ancaphylactia activity$^{2-5}$. In addition, they have been shown to act as cognitive enhancers,
for the treatment of neurodegenerative disease, including Huntington's disease, Alzheimer's
disease, amyotrophic lateral Sclerosis, AIDS associated dementia and Down's syndrome as
well as for the treatment of Schizophrenia and myoclonus$^{6,7}$. Also several biologically active
natural products contain these subunits. A number of 2-amino-4H-pyran derivatives are useful as photoactive materials, pigments, potential biodegradable agrochemicals. Thus a synthetic interest has that included methodological improvements of the original reaction conditions. The titled compounds are synthesized by reaction of malononitrile with dimedone in the presence of an appropriate aldehyde. A variety of reagents such as hexadecyltrimethylammonium bromide (HTMAB), NaBr, rare earth perfluorooctanoate (RE(PFO)), (S)-proline, Na$_2$SeO$_4$, Ce(SO$_4$)$_2$·4H$_2$O, the use of microwave irradiation, KF-basic alumina under ultrasound irradiation, tetramethylammonium hydroxide (TMAH), electrolysis, tetrabutylammonium bromide (TBABr) and amino-functionalized ionic liquid were employed to catalyze these reactions.

In spite of potential utility of aforementioned routes for the synthesis of 4-H-benzo[b]pyran derivatives many of these methods involve expensive reagents, acidic conditions, long reaction times, low yields, use of excess of reagents/catalyst and use of toxic organic solvents and complicated work-up methods. The lack of facile and general synthetic methodology under essentially natural, practical and mild reaction condition has promoted us to develop an efficient, convenient and practical procedure for the one-pot green synthesis of 4-H-benzo[b]pyrans reaction under aqueous media. to the best of our knowledge a complex catalyst has not been used in the synthesis of 4-H-benzo[b]pyrans.

Green chemistry emphasizes the development of environmentally benign chemical processes and technologies. According to the principle of safe chemistry, synthetic method should be designed to use substances that exhibit little or no toxicity to human health and environment. In this regard and in continuation of our interest on application of heterogeneous catalysts in organic reactions, we wish to report herein, a new, simple, mild and ecofriendly method for the synthesis of 4-H-benzo[b]pyrans via a one-pot three-component tandem Knoevenagel-cyclocondensation reaction using Zn(Phen)$_2$Cl$_2$ (2 mol%) as environmentally friendly homogeneous complex catalyst with high catalytic activity and reusability in very short reaction time in water base media (Scheme 1).

![Scheme 1](image-url)

**Experimental**

Melting points were determined on a gallenkamp melting point apparatus and are uncorrected. NMR spectra were recorded at 500 (1H) and 125.77 (13C) MHz on Bruker DRX-500 avance spectrometer at 500 and 125.77 MHz, respectively. All compounds were known in the literature, the NMR and IR spectra of the products were in agreement with earlier data.

**General procedure for the preparation of 4-H-Benzo[b]pyran4-H-Benzo[b]pyrans (4c)**

In a typical general procedure, a mixture of aromatic aldehyde (1 mmol), malononitrile (1 mmol) and dimedone (1 mmol) in H$_2$O (3 mL) at room temperature, were stirred thoroughly in the presence of catalytic amount of Zn(Phen)$_2$Cl$_2$ (10 mg, 2 mol%) about 5 min to afford the 4-H-benzo[b]pyrans in excellent yields. Completion of the reaction was confirmed by TLC. Then the mixture was filtered. The solid product was separated by filtration from the soluble catalyst after washing with H$_2$O. Pure 4-H-benzo[b]pyran4-H-benzo[b]pyrans (4) was obtained in 94% yield without any use of more purification. Structures of the products were confirmed from physical and spectroscopic data (IR and 1H NMR) in comparison with the literature data.
General procedure for the synthesis of Zn(phen)$_2$Cl$_2$

To a 20 mL ethanolic solution of ZnCl$_2$ (0.136 g, 1 mmol), 10 mL ethanolic solution of the 1,10-phenanthroline (0.360 g, 2 mmol) was added drop wise. The resulting white suspension was stirred at 70 °C for 24 h. The suspension was cooled, filtered and then dried at room temperature. White colored zinc complex, Zn(phen)$_2$Cl$_2$, was obtained in 89% yield. Structure of the zinc complex was confirmed from spectroscopic data (IR and Anal. Calc) in comparison with those reported literature$^{27}$: Anal. Calc. For C$_{24}$H$_{16}$N$_4$Cl$_2$Zn: C, 58.05; H, 3.22; N, 11.28. Found: C, 58.10; H, 3.19; N, 11.26%. FT-IR (KBr, cm$^{-1}$): 3046(br), 1622(m), 1579(m), 1515(s), 1427(s), 1345(m), 1223(m), 1143(s), 1092(m), 846(s), 725(s), 638(s), 577(m) and 418(m).

Results and Discussion

To show that Zn(Phen)$_2$Cl$_2$ is an efficient catalyst, we accomplished the reaction at room temperature in the absence of catalyst for 4 h. The reaction just produced alkene (a) and no benzo[b]pyran was formed (Figure 1.).

This prove the essential effect of Zn(Phen)$_2$Cl$_2$ as a mild and efficient catalyst in the progressing of the reaction. In order to improve yield, we performed reaction using different quantities of reagents. The best results was obtained with a 0.02:1:1:1.5 ratio of Zn(Phen)$_2$Cl$_2$ complex, aldehyde, dimedone and malononitrile. Also, we carried out a controlled reaction in different solvents (Table 1).

Table 1. Effect of solvents in the synthesis of 4-H-benzo[b]pyran4-H-benzo[b]pyrans (4c) using 2 mol% of Zn(Ph)$_2$Cl$_2$ complex at room temperature.

| Entry | Solvent          | Time  | Yield, % |
|-------|------------------|-------|----------|
| 1     | H$_2$O           | 5 min | 94       |
| 2     | EtOH             | 18 h  | 82       |
| 3     | CH$_2$Cl$_2$     | 24 h  | __       |
| 4     | Ethylacetate     | 24 h  | __       |
| 5     | 1,2-Dichloroethene | 24 h | __       |

As shown in Table 1, for this type of reaction, a polar solvent is generally needed to obtain high yields with low mole percentages of catalyst in mild reaction conditions. The result suggests that H$_2$O at room temperature condition is the better reaction system than the organic solvents media.

To investigate the versatility of the catalyst, the reaction of dimedone, malononitrile and various aromatic aldehydes was carried out in H$_2$O at room temperature using 2 mol% of Zn(Phen)$_2$Cl$_2$ (Table 2).

Table 2. 4-H-Benzo[b]pyrans derivatives containing electron-withdrawing groups such as nitro and halide groups or electron-donating groups such as hydroxyl and alkoxy groups (Table 2) were formed in a short experimental time (5 min) with excellent yields (90%-100%).

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It is also noticed that the condensation using Zn(Ph)$_2$Cl$_2$ complex proceeds rapidly and is superior to the reported procedures. This claim is justified through the representative examples, illustrated in Table 3.
Table 2. Synthesis of 4 catalyzed by Zn(Phen)$_2$Cl$_2$ at ambient temperature in water as solvent

| Product | Ar | yield (%)$^a$ | mp, ºC | Mp., reported$^{[19]}$ |
|----------|-----|---------------|--------|------------------|
| 4a       | C$_6$H$_5$ | 90 | 222-224 | 226-228$^{[19]}$ |
| 4b       | 4-Br- C$_6$H$_4$ | 91 | 207-209 | 203-205$^{[18]}$ |
| 4c       | 4-Cl- C$_6$H$_4$ | 94 | 208-209 | 207-209$^{[17]}$ |
| 4d       | 2,4-Cl$_2$-C$_6$H$_3$ | 96 | 178-179 | 180-182$^{[16]}$ |
| 4e       | 3-O$_2$N- C$_6$H$_4$ | 97 | 207-209 | 208-211$^{[19]}$ |
| 4f       | 3-OH- C$_6$H$_4$ | 93 | 231-233 | 236-238$^{[19]}$ |
| 4g       | 3-H$_3$C-C$_6$H$_4$ | 99 | 212-214 | 214-216$^{[19]}$ |
| 4h       | 2-Cl- C$_6$H$_4$ | 100 | 209-210 | 200-202$^{[17]}$ |
| 4i       | 3-H$_3$CO- C$_6$H$_4$ | 93 | 188-190 | 186-187$^{[17]}$ |
| 4j       | 4-H$_3$CO- C$_6$H$_4$ | 90 | 122-124 | 122-125$^{[28]}$ |

$^a$Yields refer to the isolated products

Table 3. Synthesis of 2-amino-4-(4-chlorophenyl)-3-cyano-7,7-dimethyl-5-oxo-4H-5,6,7,8-tetrahydrobenezopyran using different reagents and reaction conditions

| Entry | Reagent | Conditions | Time | yield(%)$^{ref}$ |
|-------|---------|------------|------|-----------------|
| 1     | NaBr, 0.4 mmol | MW(Power: 60), 70 ºC | 10 min | 90$^{[12]}$ |
| 2     | Na$_2$SeO$_4$, 0.1 g | EtOH/H$_2$O, reflux | 3h | 90$^{[16]}$ |
| 3     | TMAH, 10 mol% | H$_2$O, r.t | 0.5-2 h | 83$^{[20]}$ |
| 4     | ___ | electrolysis (10 mA) | 4-5 h | 95$^{[17]}$ |
| 5     | TBABr, 10 mol% | H$_2$O, reflux | 2 h | 91$^{[22]}$ |
| 6     | Ce(SO$_4$)$_2$.4H$_2$O, 2.5 mol% | EtOH/H$_2$O, 45ºC | 30 min | 90$^{[17]}$ |
| 7     | Zn(Phen)$_2$Cl$_2$ | H$_2$O, r.t | 5 min | 94$^{Present work}$ |

$^a$Yields refer to the isolated products; r.t: room temperature

**Reusability of Zn(Phen)$_2$Cl$_2$**

The reusability of the catalysts is one of the most important benefits and makes them useful for commercial applications. Thus the recovery and reusability of Zn(Phen)$_2$Cl$_2$ was investigated. Fortunately, the precipitated material in the reaction shown in Scheme 1 was successfully recycled three times. The catalyst could be recycled in two ways.

**Method A**

In the first method, the reaction mixture was filtered and washed with H$_2$O. The soluble catalyst was easily reused after distillation of solvent, washing with CHCl$_3$ and drying at room temperature. The recycled catalyst could be examined in next run in the reaction between 4-chlorobenzaldehyde, malononitrile and dimedone.

**Method B**

In the second method, the reaction mixture was filtered and the solid product was washed with H$_2$O. Zn(Phen)$_2$Cl$_2$ complex is soluble in water. The remaining solution including soluble catalyst could be reused as such for subsequent experiments (up to 3 cycles). In the next run, 4-chlorobenzaldehyde, malononitrile and dimedone was added to the filtered solution to afford the comparable yields of the product as shown in Figure 2.
Figure 2. The reusability of the catalyst in the synthesis of 4-\textit{H}-benzo[b]pyran4-\textit{H}-benzo [b]pyrans (4c).

It was interesting to note that the Zn(Ph)$_2$Cl$_2$ could be reused in three cycles via this method without any loss of its activity, more purification, distillation of solvent and dry catalyst. Thus the remained mixture of the reaction could be used several times to produce the 4-\textit{H}-benzo[b]pyran derivatives with simple work-up and not using cumbersome apparatus for recycling of the catalyst. A little increase in reaction time is attributable to the mechanical loss of some of the 10 mg of catalyst used, increase in volume of solvent or some combination of these factors. Also, a little increase was observed in the product yields. It could be because of the soluble and remaining products from the previous run. So, this improved procedure could be used to obtain the products with more efficiency. The presented procedure is continual, very simple and clean, environmentally friendly due to use water as green solvent, cost effective, more efficient and easier work-up than reported methods. Also, the product could be obtained continual in the same solvent environment.

Conclusion

In conclusion, the present method is an operationally simple and environmentally friendly procedure for the synthesis of compound 4 using catalytic amount of Zn(Phen)$_2$Cl$_2$ at ambient temperature. In addition recyclability and moderate Lewis acidity of the catalyst, safe conditions, cost effective, excellent yields of products without any use of more purification, very short reaction time and use of water as a green solvent make this methodology a valid contribution to the existing processes in the field of 4-\textit{H}-benzo[b]pyrans derivatives synthesis. To the best of our knowledge, this procedure provides the first example of complex catalyzed the efficient synthetic method for 4-\textit{H}-benzo[b]pyrans derivatives.

Acknowledgment

We thank the Khoramshahr Marine Science and Technology University, for partial financial support of this investigation.

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