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Eco-Friendly Hydrotalcite Recyclable Catalysts using Efficient Synthesis of 3,4-Dihydropyrimidin-2(1H)-Thiones

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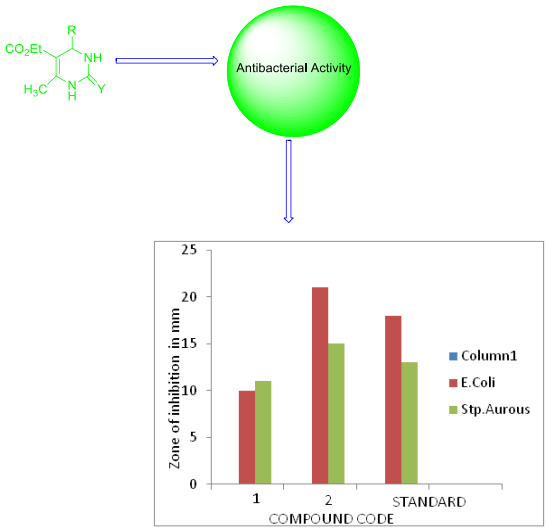
Abstract

For the multi-component one-pot synthesis of dihydropyrimidinone, a hydrotalcites (HT) catalyst was used. Nitrogen-containing heterocycles are the most essential compounds in medicinal chemistry, as they exhibit a broad range of biological activities. The current study focuses on the environmentally favorable synthesis of 3,4-dihydropyrimidine-2(1H)-thione (DHPMT) in the presence of different hydrotalcite catalysts under mild conditions. Thus, prepared compounds are analysed by InfraRed spectroscopy (IR), ^{1}H NMR and ^{13}C NMR Spectroscopy. When the compounds were tested for antibacterial activity, compound 2 performed well when compared to the normal. Higher yields, shorter reaction times, and a quicker set-up are all advantages of this green synthetic form. The easy reusability of biocompatible catalysts makes this protocol is an attractive, cost-effective and eco-friendly.



Keywords: *HT, DHPMT, Biginelli reaction, Multicomponent reaction, Antibacterial activity*

Introduction

The use of solid catalysts in base-catalysed reactions has piqued the interest of the fine-chemical industry in recent years.[1-3] The majority of the effort is focused on developing new natural or synthetic organic compounds.[4] In medicinal chemistry, the heterocyclic nucleus plays an important role and acts as a primary template for the synthesis of various therapeutic agents.[5] Pyrimidine (Py) is a six-membered cyclic compound of four carbon and two nitrogen atoms, it is not pharmacologically active but they are very important to prepare many synthetic derivatives in the development of modern medicine.[6] (DHPM) are heterocyclic structures with high pharmacological activity and a wide range of antiviral, antitumor, antibacterial. and anti-inflammatory properties. Several marine natural products with the dihyropyrimidine-5-carboxylate core structure, such as the banzelladine alkaloids, have been discovered to be effective HIV gp – 120-CD4 inhibitors. Calcium channel blockers, antiviral and anti-tumor agents, and antagonists are all used by polyfunctional DHPMs.[7]

Biginelli identified the first access to these biologically active DHPMs scaffold in 1893[8]. In recent years, the synthesis of DHPM is achieved by using microwave irradiation, ultrasound irradiation[9], and ionic liquids[10] to strengthen and alter this reaction. The various Lewis acids are used in a catalytic development for the synthesis of 3,4-dihydropyrimidine-2(1H)-thiones [11-13]. Using ILs such as [BMIM] [$FeCl_4$][14] and [BMIM]BF_4-immobilized Q (II) acetyl acetonate[15], some research groups were able to obtain 3,4-dihydropyrimidin-2(1H)-thiones. The expeditiously modified Biginelli reaction[16] has recently been used with 1-sulfopyridinium chloride.

The Biginelli reaction is a well-known, easy-to-follow method for the production of 3,4-dihydropyrimidinone (3,4-DHPM) from the three-component condensation of an aliphatic or aromatic aldehyde-ketoester and urea [17]. Liquid-phase hydroxylation of phenol using H_2O_2 as an oxygen source, using copper(II)-containing HT.[18]

Furthermore, solid-supported reagents have the advantage of being easily rescue from the reaction medium through filtration and reusable after activation, making the process as an economically feasible. Anionic clays are the most attractive heterogeneous catalysts due to their reusability, environmental compatibility, inexpensive, non-toxicity and easy to manipulate. From the above literature survey, our research is focusing the creation of new synthetic methods, we present here a new mild and effective synthesis technique also.

2. Experimental

2.1 General

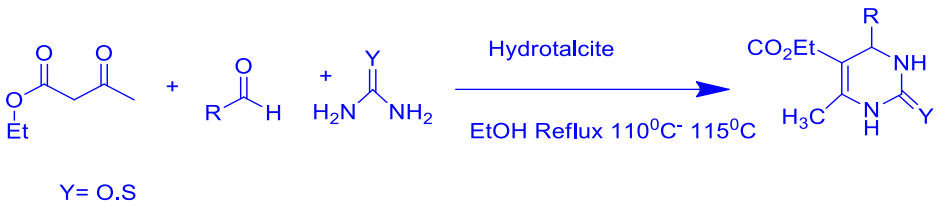
All the compounds were generated and analysed. Both solvents and chemicals were purchased commercially and used exactly as they were given to us. Only characteristic peaks were recorded in the IR spectra of the compounds, which were obtained using the FT-IR Bruker α-T model. The compounds were analysed using ^{1}H and ^{13}C NMR on a Bruker AMX 400 MHz NMR with TMS as an internal norm. Deuterated Dimethyl Sulfoxide was used as the solvent. All reactions were tracked using silica Gel-G TLC plates, with spots visible using iodine vapours or ultraviolet light irradiation (254 nm). By using disc diffusion method, the antimicrobial activity was tested in the microorganisms of (E. coli, staphylococcus) and standards (chloramphenicol, streptomycin)

2.2. Preparation of Hydrotalcites (HT)

$Al(NO_3)_3.9H_2O$ (0.01M) and $Mg(NO_3)_2.6H_2O$ (0.05M) were dissolved in deionized water (100mL) and slowly applied to a second solution of Na_2CO_3 (0.03M) and NaOH (60mL) (0.07M). With intense stirring, the resulting mixture was heated to 650°C for 18 hours. After cooling to room temperature (RT), the white color solution was filtered, washed thoroughly with deionized water and dried at 110°C overnight. TGA-DTA analysis revealed two endothermic transitions, which were used to characterize them. As previously mentioned,[19], The first transition occurred at a lower temperature (149°C), corresponding to a loss of chemically absorbed water molecule, and the second transition occurred at a higher temperature (413°C), which corresponded to a removal of hydroxyl groups and carbonate decomposition. Powder XRD patterns were used to characterize HT, and they were found to be identical to those previously described[19], with an interlayer spacing (d003) of 0.78 nm, suggesting the presence of carbonate ions in the tertile.

2.3 Standard procedure for the hydrotalcite catalysed using Biginelli reaction

In a 50ml round bottomed flask reflux / magnetic stirring, a mixture of aromatic aldehyde (2mmol), ethyl acetoacetate (2mmol), urea or Thiourea (3mmol), hydrotalcite (500mg), and 10 ml ethanol were heated between 110°C and 115°C for 4 hours and cool to room T. After it was diluted with cold water to dissolve any excess urea or thiourea, and then filtered. TLC was used to track the reaction's completion using petroleum ether-ethyl acetate (8:2) as the eluent. After removing the excess solvent, the mixture was recrystallized with ethanol as the solvent, and the products were produced. In Scheme 1, the structures of all synthesized compounds are depicted.



Scheme 1: Synthesis of Compounds

Results and Discussion

To determine the catalytic efficiency of hydrotalcite used for the synthesis of Biginelli 3,4-dihydropyrimidin-2(1H)-thiones, a series of reactions between benzaldehyde, ethyl acetoacetate, and urea/thiourea at room temperature was investigated using hydrotalcite. The results show that there is no critical outcome when a catalyst is present (Table 1 entry 1,2). When the catalytic activity of Co and Mg is compared to the reaction of a thio substituted compound with good reactivity, the destined product is obtained in 92 percent of the time. IR, ^{1}H NMR, and ^{13} C NMR analysis were used to identify and classify all the synthesized compounds.

Table1: Effect of catalyst of DHPMs

Entry	R^1	R^2	X	Method	Catalyst	Time[a](h)	Colour	Yield (%)
1	**C_6H_5**	**OEt**	**O**	**Stir/ Reflux**	Mg-Al, Co-Al	**4**	**Colourless**	**65**
2	**C_6H_5**	**OEt**	**S**	**Stir/ Reflux**	Mg-Al, Co-Al	**4**	**Colourless**	**92**

[a]*In a typical experiment, aromatic aldehyde(2mmol), ethyl acetoacetate (2mmol), urea or thiourea (3mmol), Hydrotalcite (500mg) and ethanol(10ml) are used.*

3,4-dihydropyrimidin-2-(1H)-one (Table1,Entry1): Colourless solid; Yield 65%; IR (KBr):3244,2933,1728 cm^{-1}; ^{1}HNMR($CDCl_3$,300MHz):δ (1.078-1.11)(t,1H), δ (1.501) (s,6H), δ(2.288) (s,1H),δ (3.99-4.02) (d,1H),δ (5.33-5.34) (s,1H), δ (7.19-7.25) (m,4H); ^{13}C NMR($CDCl_3$,75MHz): 14.14, 18.59, 55.68, 59.99, 76.59, 77.02, 77.44, 101.28, 126.58, 127.94, 128.66, 143.72, 146.39, 153.51, 165.64; E. Coli (mm):10 Staphylococcus Aurous (mm):11

3,4-dihydropyrimidin-2-(1H)-thione (Table1,Entry2): Colourless solid; Yield 92%; IR (KBr):3113,2996,1647 cm^{-1}; ^{1}HNMR($CDCl_3$,300MHz):δ (1.17-1.21 t,3H), δ (1.22) (s,2H), δ (2.36) (s,3H) δ (4.05-4.13) (t,2H), δ (5.40-5.41) (s,1H), δ (6.99) (s,1H), δ (7.26-7.35) (m,5H), δ (7.54) (s,1H); ^{13}C NMR($CDCl_3$,75MHz): 14.14, 18.59, 55.68, 59.99, 76.59,

77.02, 77.44, 101.28, 126.58, 127.94, 128.66, 143.72, 146.39, 153.51, 165.64; E. Coli (mm):21 Staphylococcus Aurous (mm):15

Antibacterial Activity:

The agar-diffusion method was used to evaluate antimicrobial activity. The synthesized compounds are tested in vitro against Gram-positive Staphylococcus aureus and Escherichia coli (Gram-negative). Nutrient agar and potato dextrose agar 20 were used as media. As a reference standard, streptomycin was used. Both bacteria were incubated for 48 hours at 37 °C overnight. Using a Vernier scale, the petri plates were examined after the incubation time to look for zones of inhibition. The findings were assessed by contrasting the derivatives' zone of inhibition to that of the standard drug. Antimicrobial treatment was then performed (Table 2). When compared to normal, compound 2 with thio substitution has strong antimicrobial activity

Table 2. Antimicrobial Activities of synthesised compounds

Entry	E. COLI (mm)	STAPHYLOCOCCUS AUROUS (mm)
1	10	11
2	21	15
Standard	18	13

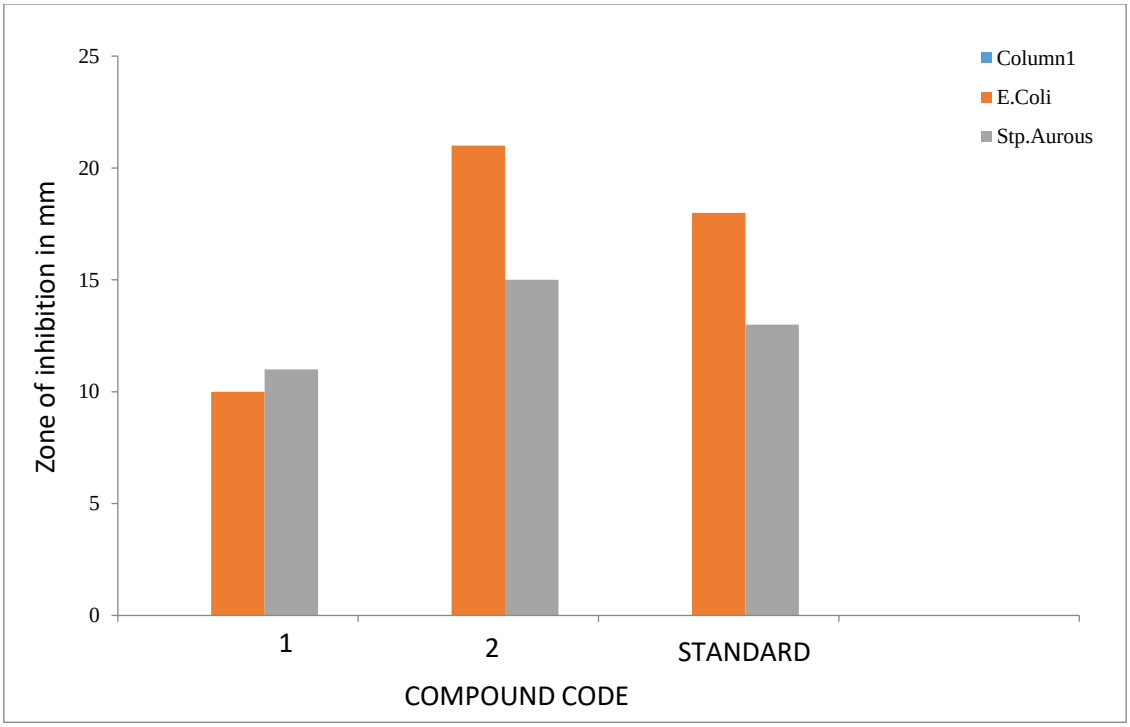


Fig 1. Antibacterial Activity

Conclusion

From the above study, the important points are presented here as conclusions. The synthesis of 3,4-dihydropyrimidine-2(1H)-thione (DHPMT), hydrotalcite was found to be a safe, operationally simple, non-volatile, thermally nontoxic, and recyclable catalyst. Physical, analytical and biological methods were used to test all of the 3,4-Dihydropyrimidin-2-thione derivatives that were synthesized. Antibacterial activities were tested on all of the compounds. As opposed to normal, compound 2 has strong antibacterial activity against E. coli and S. aureus.

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