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Zinc oxide-acetyl chloride as an efficient catalyst for the one-pot preparation of Knoevenagel condensation of aromatic aldehydes with 1,3-dimethylbarbituric acid

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Abstract: A convenient method containing a new, one-pot, two component condensation of 1,3-dimethyl-barbituric acid and benzaldehyde for the preparation of Benzylidene barbituric acid derivatives is reported using ZnO-Acetyl Chloride as a catalyst. This method has the advantages of high yields, simple methodology and easy workup.

Keywords: Knoevenagel; Benzylidine barbituric acid; ZnO-acetyl chloride.

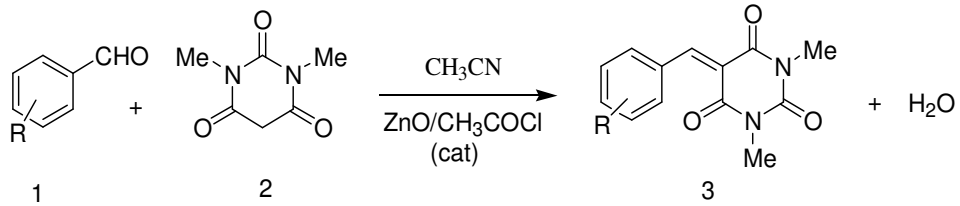
Introduction

The Knoevenagel condensation reaction has been extensively studied since its initial report in 1894 [1]. There has been a tremendous amount of research focusing on all aspects of this condensation process. The Knoevenagel condensation of aldehydes with active methylene compounds is an important and widely employed method for carbon–carbon bond formation in organic synthesis [2] with numerous applications in the synthesis of fine chemicals [3], hetero Diels–Alder reactions [4] and in synthesis of carboxylic as well as heterocyclic [5] compounds of biological significance. The reactions are usually catalyzed by bases [6] such as amines, ammonia or sodium ethoxide in organic solvents. Lewis acids [7], surfactants [8], zeolites [9], heterogeneous catalysts [10] and ionic liquids [11]. In recent years, zinc oxide (ZnO) has gained much interest in the synthesis of nitriles from aldoximes [12], the Beckmann rearrangement [13], Friedel–Crafts acylation [14] and the acylation of alcohols, phenols and amines [15]. Zinc oxide is an inexpensive, moisture stable, reusable, commercially available and environmentally benign catalyst which has been previously employed used in Beckmann rearrangements [16], Friedel– Crafts acylation [14], the synthesis of cyclic ureas [17], dehydration of aldoximes [12] and oxidation of alcohols [18].

Results and discussion

In the present work, we now describe a very simple and highly efficient method for the condensation of various aldehydes 1 with 1,3-dimethylbarbituric acid 2 as an active methylene compound. (Scheme 1)

Scheme 1



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Initially, benzaldehyde was reacted with 1,3-dimethylbarbituric acid in the presence of ZnO-Acetyl Chloride in acetonitrile as solvent at 80°C under reflux to give the corresponding Benzylidine barbituric acid in 98% yield. Several aldehydes were subjected to this procedure to give the corresponding Benzylidine barbituric acid in high to excellent yields. The results are summarized in Table 1. The structures of products were deduced from the IR and NMR (^{1}H and ^{13}C). We optimized the amount of zinc oxide in the reaction between benzaldehyde, acetyl chloride and acetonitrile. The optimum amount of ZnO was found to be 20 mol %. As shown in Table 1 aromatic aldehydes with both electron-withdrawing or donating substituents and 1,3-dimethylbarbituric acid produced Benzylidene barbituric acids without the formation of any side products, in high to excellent yields at reflux (Table 1 entries 1–14). Use of ketones did not yield any of the desired condensation products (entries 15 and 16). Thus, we prepared a range of Benzylidene barbituric acids under the following optimized reaction conditions: aldehyde (1 equiv), 1,3-dimethylbarbituric acid (1 equiv), acetyl chloride (1 equiv) and acetonitrile (8 ml) as solvent.

Table 1. Preparation of benzylidene barbituric acids from aldehydes and 1,3-dimethylbarbituric acid in the presence of acetonitrile catalyzed using ZnO-Acetyl Chloride.

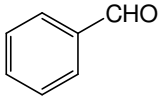
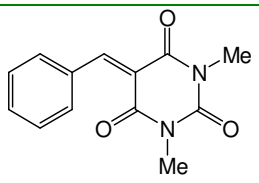
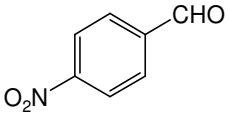
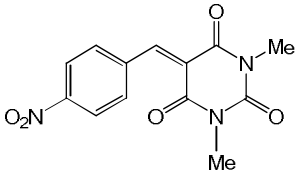
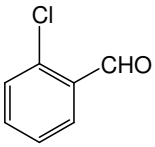
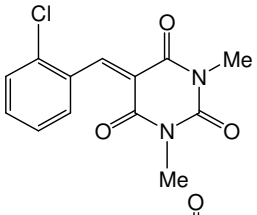
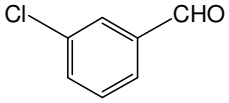
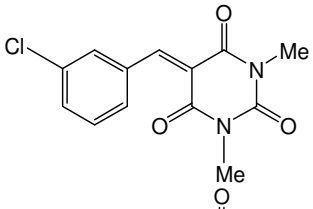
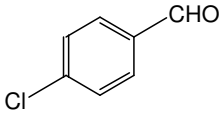
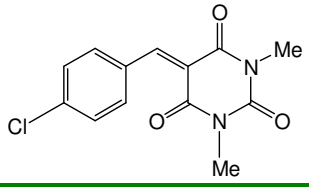
Entry	Aldehyde	Product	Yield (%)	M.P °C[19-23]
1			98	159-160
2			95	190-193
3			89	95-97
4			94	137-140
5			96	154-156

Table 1. *continued*

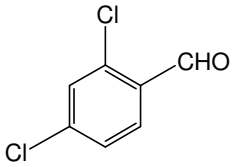
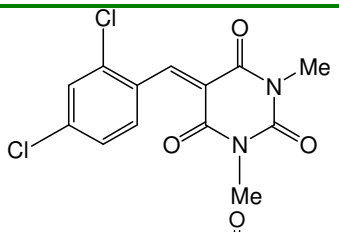
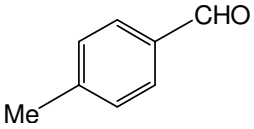
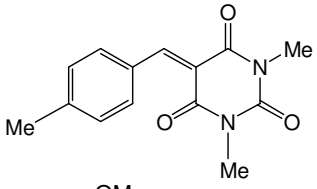
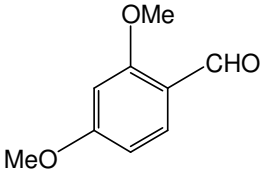
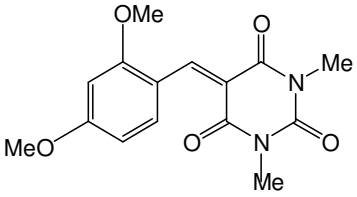
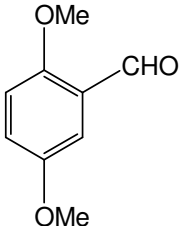
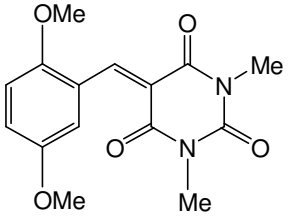
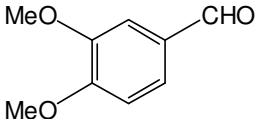
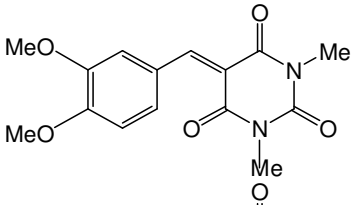
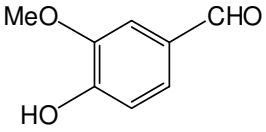
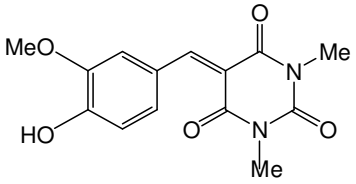
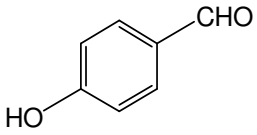
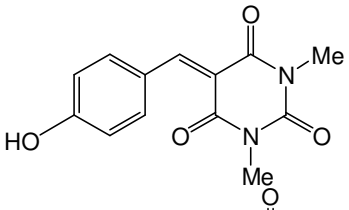
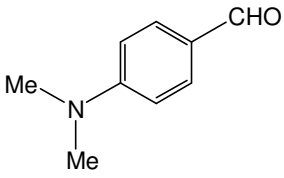
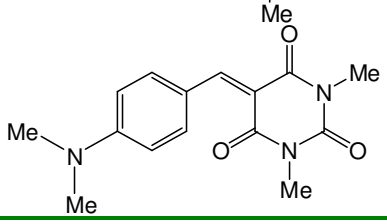
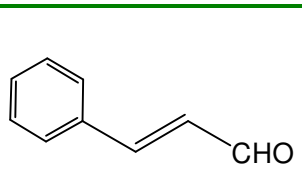
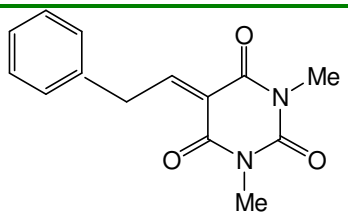
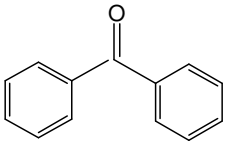
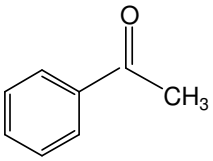
6			98	177-179
7			90	126-129
8			83	200-203
9			86	138-141
10			88	216-219
11			89	223-225
12			92	297-298
13			89	231-233

Table 1. *continued*

14			78	195-197
15		……..	….	……
16		……..	…..	……

Experimental

General. Melting points were measured on an Electrothermal 9100 apparatus. IR spectra were measured on a Shimadzu IR 460 spectrometer. The ^{1}H and ^{13}C NMR specra were measured with BRUKER DRX-500 AVANCE instrument at 500 and 125.7 MHz, respectively.

General experimental procedure for preparation of Benzylidene barbituric acids:
A solution of the aryl aldehyde (1 equiv), 1,3-dimethylbarbituric acid (1 equiv), acetyl chloride (1 equiv), acetonitrile (8 mL) and ZnO (20 mol %) was heated at 80 $^{\circ}C$ under reflux. The reaction mixture was stirred for the appropriate time (Table 1). The progress of the reaction was followed by TLC. After completion of the reaction, the mixture was cooled and poured into 20 mL of ice-water. The solid residue was separated and dissolved in dichloromethane. The solution was filtered and zinc oxide was isolated and could be reused. The organic phase was absorbed on silica gel and purified by column chromatography petroleum ether/ethyl acetate (9/1).
Selected Specteral data as a typical is given below:

1,3-Dimethyl-5-(4-Nitrobenzylidene)-barbituric acid (Table 1, entry 2)
Mp: 190-193; IR (KBr): υ= 1697, 1628, 1542, 1519, 1474, 1383, 1347, 1205, 854 cm^{-1}. ^{1}H NMR (500 MH_Z, $CDCl_3$), δ= 8.57 (s, 1H), 8.28 (2H, d, *J*= 8.7), 7.95 (2H, d, *J*= 8.6), 3.44 (s, 3H), 3.36 (s, 3H). ^{13}C NMR (125 MH_Z, $CDCl_3$): δ= 28.56, 29.19 (2, N-CH_3), 120.70 (OC-*C*-CO), 123.14, 132.16 ($C_{aromatic\ ring}$), 139.08 (C-NO_2), 148.89 (C_{arom}), 150.85 (CO-N), 155.35 (C_{alken}), 159.70, 161.40 (2 CO).

Acknowledgement

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