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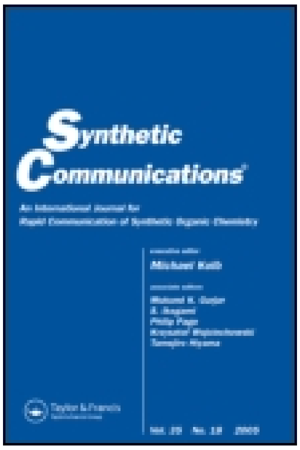

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An Efficient and Environmentally Friendly Method for Synthesis of 3,4-Dihydropyrimidin-2(1H)-ones Catalyzed by $Bi(NO_3)_3 \cdot 5H_2O$

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An Efficient and Environmentally Friendly Method for Synthesis of 3,4-Dihydropyrimidin-2(1H)-ones Catalyzed by $Bi(NO_3)_3 \cdot 5H_2O$

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ABSTRACT

Bismuth nitrate pentahydrate catalyzes the three component condensation reaction of an aromatic aldehyde, urea and a β-ketoester or a β-diketone under solvent-free conditions to afford the corresponding dihydropyrimidinones (DHPMs) in high yields. The present method is also effective for the selective condensation of aryl aldehydes in the presence of aliphatic aldehydes.

Key Words: Aldehydes; Lewis acids; Catalysts; Biginelli; $Bi(NO_3)_3 \cdot 5H_2O$.

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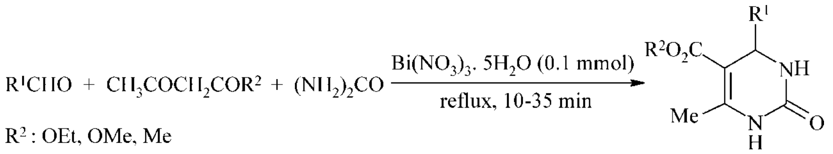
INTRODUCTION

As green chemistry has become a major concern to organic chemists in present years, reactions under solvent-free conditions with a solid catalysts have received much attention. These reactions offer several advantages in preparative procedures such as environmentally friendly, simplifying work-up, formation of cleaner products, enhanced selectivity, and much improved reaction rates.[1]

Dihydropyrimidinones (DHPMs) are important classes of heterocycles that have attracted much synthetic interest and their derivatives have pharmacological and biological properties, as the antihypertensive agents, calcium channel blockers, α-1a-antagonists, neuropeptide Y(NPY) antagonists, antitumor, antibacterial, and antiinflammatory behaviors.[2–5] Recently, the batzelladine alkaloids containing the dihydropyrimidinone-5-carboxylate core, are the most notably, which have been found to be potent HIV-gp-120-CD4 inhibitors.[6] In addition, due to the importance of these compounds as synthons in organic synthesis many synthetic methods for preparing such compounds have been developed and Biginelli reaction has gained an active ongoing research.[7] However, there are several disadvantages associated with these methodologies including unsatisfactory yields, long conversion times, difficult handling of reagents, toxic and inflammable organic solvents, and incompatibility with other functions in the molecules that limited these methods to small-scale synthesis. Thus, development of facile and environmental friendly synthetic methods to the DHPMs, is demanded.

The application of bismuth(III) salts as catalysts in organic synthesis has been investigated extensively.[8,9] In line with the recent surge in activity in the use of $Bi(NO_3)_3 \cdot 5H_2O$,[10] we now report a simple, efficient, selective, and environmentally benign method for the synthesis of 3,4-dihydropyrimidin-2-ones from aryl aldehydes with β-dicarbonyl compounds and urea under solvent-free conditions (Sch. 1).

Various substituted aromatic aldehydes reacted well with β-dicarbonyl compounds and urea in the presence of a catalytic amount of $Bi(NO_3)_3 \cdot 5H_2O$ under solvent-free conditions to give the corresponding DHPMs in 78–97% yields (Table 1).



Scheme 1.

Table 1. Formation of DHPMs[a] catalyzed by $Bi(NO_3)_3 \cdot 5H_2O$ under solvent-free conditions.

Entry	R_1	R_2	Time (min)	Yield (%)[b]	M.p. (°C)	
					Found	Reported
1	C_6H_5	OEt	10	96/89[c]	202–203	203–204[7c]
2	$4\text{-}CH_3C_6H_4$	OEt	10	91	169–171	170–171[7h]
3	$4\text{-}CH_3OC_6H_4$	OEt	10	90/87[c]	201–202	201–203[7c]
4	$4\text{-}NMe_2C_6H_4$	OEt	10	95	257–269	256–258[7b]
5	$3\text{-}OHC_6H_4$	OEt	25	90	213–212	213–215[7f]
6	$4\text{-}OH, 3\text{-}CH_3OC_6H_3$	OEt	10	87	231–232	232–233[7c]
7	$2\text{-}NO_2C_6H_4$	OEt	30	78	207–209	206–208[7i]
8	$3\text{-}NO_2C_6H_4$	OEt	10	92	227–228	226–227[7c]
9	$4\text{-}NO_2C_6H_4$	OEt	25	85	210–211	209–210[7c]
10	$4\text{-}FC_6H_4$	OEt	10	90	175–177	175–177[7g]
11	$4\text{-}ClC_6H_4$	OEt	10	90/86[c]	213–215	212–214[7c]
12	$2,4\text{-}Cl_2C_6H_3$	OEt	30	80	249–251	249–250[7b]
13	$CH_2{=}CHC_6H_4$	OEt	30	83/79[c]	233–234	232–235[7g]
14	α-Naphthyl	OEt	20	80	247–249	247–248[7h]
15	C_6H_5	OMe	10	93	212–214	210–212[7c]
16	$4\text{-}CH_3OC_6H_4$	OMe	10	91	195–196	194–195[7c]
17	$4\text{-}CH_3C_6H_4$	OMe	10	90	202–203	202–204[7a]
18	$4\text{-}NO_2C_6H_4$	OMe	25	85	237–239	236–238[7c]
19	$4\text{-}ClC_6H_4$	OMe	10	92	204–206	203–205[7c]
20	C_6H_5	Me	10	97/95[c,d]	233–235	233–236[7g]
21	$4\text{-}CH_3OC_6H_4$	Me	20	83[d]	169–170	168–170[7g]
22	$4\text{-}O_2NC_6H_4$	Me	20	82[d]	233 (dec)	230 (dec)[7g]
23	$2\text{-}O_2NC_6H_4$	Me	30	79[d]	227 (dec)	225 (dec)[7e]

[a] All products were characterized by comparison of their physical and spectral data with those of authentic samples.
[b] Isolated yields.
[c] Isolated yields with reused catalyst.
[d] Under 60°C was performed.

Most importantly, aromatic aldehydes carrying either electron-donating or electron-withdrawing substituents reacted very well and gave good to excellent yields. Aliphatic aldehydes were also used in Biginelli reaction, but their yields were not satisfactory even after 3 h. In fact, more than 70% of the parent aldehydes were recovered and only less than 30% of the desired products obtained. Acid-sensitive substrates like cinnamaldehyde are also reacted in high yields without the formation of any side products.

The tolerance of various functional groups under the present reaction conditions has been examined by reacting the substrates bearing methoxy, nitro, hydroxy, and olefinic groups. In comparison, this reaction was examined in different solvents and indicated that the reaction was performed better in neat conditions (Table 2).

In order to show the selectivity of the desired method we have also investigated the competitive reactions in the presence of this catalyst and found that aromatic aldehydes react selectively in the presence of aliphatic aldehydes (Sch. 2).

Under the reaction conditions employed, thiourea did not undergo the Biginelli reaction and the starting materials were recovered unchanged. These may be considered as a useful practical achievement in Biginelli reaction. Moreover, this catalyst has been recovered almost quantitatively and has been reused for second cyclocondensation reaction and the yields of the second runs were comparable to those of the first run (Table 1, products 1, 3, 11, 13, and 20).

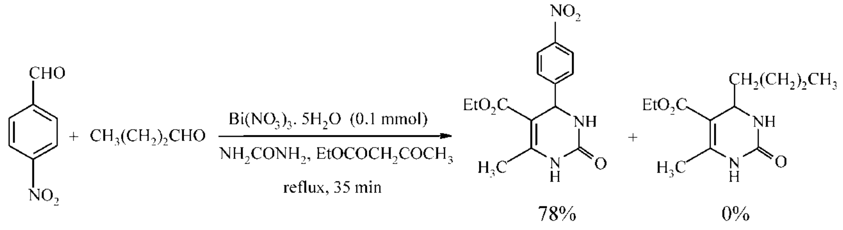
In conclusion, we have demonstrated the use of $Bi(NO_3)_3 \cdot 5H_2O$ as a low toxic, inexpensive, oxygen and moisture tolerant catalyst that could be readily recovered and reused for the one-pot formation of DHPMs under solvent-free conditions. In addition, high chemoselectivity, low reaction times, high yields of the products, easy work-up, and ecologically clean procedure, make the present method as a useful addition to the present methodologies.

EXPERIMENTAL

Products were characterized by comparison of their spectral data (^{1}H-NMR, IR) and physical data with those reported in the literature.

Table 2. Formation of DHPMs in different solvents and no solvent.

Entry	Solvent	Time (hr)	Yield (%)
1	Methanol	4	75
2	Ethanol	4	80
3	Water	2	5
4	Ethanol/water (1 : 1 v/v)	4	25
5	Acetonitrile	5	55
6	Dichloromethane	5	40
7	Solvent free	0.16	90



Scheme 2.

General Procedure for the Preparation of DHPMs

To a solution of aryl aldehyde (1 mmol), β-dicarbonyl compound (1 mmol) and urea (1.3 mmol) was added $Bi(NO_3)_3 \cdot 5H_2O$ (0.1 mmol). The mixture was stirred at reflux conditions for an appropriate time (Table 1). After completion of the reaction, as indicated by TLC, ethanol (20 mL) was added, filtered and the filterate cooled until the product was crystallized. The product was washed with a mixture of (1 : 1) water/ethanol and then dried. The pure product was obtained by recrystallization from ethanol in 78–97% yields. The catalyst was washed with 95% ethanol and reused for another reaction.

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