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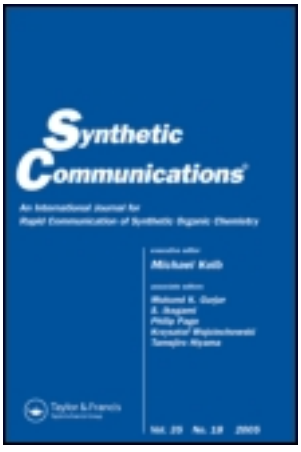

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$ZrOCl_2 \cdot 8H_2O$ as an Efficient Reagent for the Solvent-Free Synthesis of 3,4-Dihydropyrimidin-2-(1H)-ones

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Abstract: $ZrOCl_2 \cdot 8H_2O$, a commercially available reagent, can be used for the promotion of the synthesis of 3,4-dihydropyrimidin-2(1H)-ones under solvent-free reaction conditions. All reactions were performed at 90°C in good to high yields.

Keywords: Aldehydes, Biginelli condensation, 3,4-dihydropyrimidin-2(1H)-ones, solvent-free reactions, $ZrOCl_2 \cdot 8H_2O$

Because of their therapeutic and pharmacological properties and also because of the presence in their structures of several biologically active marine alkaloids,[1–4] synthesis of 3,4-dihydropyrimidin-2(1H)-ones and -thiones (DHPMs) has attracted considerable attention in recent years. The classical method for the synthesis of these types of compounds involves a one-pot, three-component condensation of β-dicarbonyl compounds with aldehydes

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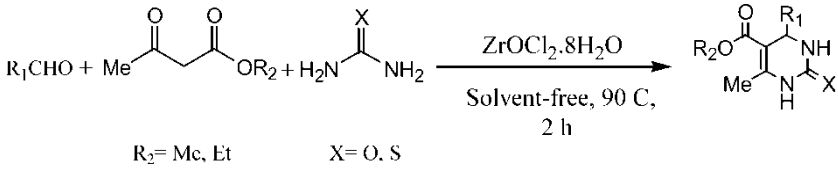
and urea or thiourea in ethanol under strongly acidic conditions.[5] This method suffers from long reaction times, acidic reaction conditions, and unsatisfactorily low yields in cases of aliphatic and some substituted aromatic aldehydes. Therefore, several improved procedures for the preparation of DHPMs, by modification of the classical one-pot approach and complex multistep strategies, have been reported during the past years.[6–16] However, the practical application of these methods suffers from disadvantages such as the use of expensive or less easily available reagents, vigorous reaction conditions, prolonged standing, and tedious manipulations to isolate the products. Therefore, a need still exists for efficient and simple protocols whereby DHPMs may be obtained under milder conditions.

In recent years, organic reactions under solvent-free conditions have attracted attention because of their enhanced selectivity, milder reaction conditions, much improved reaction rates, formation of cleaner products, and associated ease of manipulation.[17] In continuation of our ongoing research program on organic solvent-free reactions,[18–20] we have found that $ZrOCl_2 \cdot 8H_2O$, a stable and commercially available reagent, has received little attention in organic chemistry.[21,22] Herein, we report that $ZrOCl_2 \cdot 8H_2O$ is able to improve the Biginelli condensation reaction under solvent-free conditions (Scheme 1).

Optimization of the reaction conditions is carried out by the condensation of benzaldehyde, ethyl acetoacetate, and urea under solvent-free conditions. The best result was achieved by carring out the reaction of benzaldehyde, ethyl acetoacetate, and urea (with 1 : 1 : 1.5 mol ratio) in the presence of 0.1 mol of $ZrOCl_2 \cdot 8H_2O$ at 90°C for 2 h under solvent-free conditions (Table 1, entry 1).

Aliphatic and other substituted aldehydes were also reacted under the same reaction conditions to produce the corresponding DHPMs in good to high yields (Table 1). Methyl acetoacetate and thiourea were also used with similar success to provide the corresponding 3,4-dihydropyrimidin-2(1H)-thiones.[23]

In conclusion, $ZrOCl_2 \cdot 8H_2O$ can be applied as an efficient reagent for the synthesis of 3,4-dihydropyrimidin-2(1H)-ones and -thiones. The main advantages of this methodology are high yields, easy synthetic procedure, and mild and solvent-free reaction conditions. We believe that this method can be a useful addition to the present methodologies for the synthesis of 3,4-dihydropyrimidin-2(1H)-ones and -thiones.



Scheme 1.

Table 1. Solvent-free synthesis of 3,4-dihydropyrimidin-2(1H)-ones and -thiones in the presence of $ZrOCl_2 \cdot 8H_2O$[a]

Entry	R_1	R_2	X	Yield (%)[b]	Mp (°C)	Lit. mp (°C)
1	C_6H_5	Et	O	95	204–206	202–204[13]
2	4-ClC_6H_4	Et	O	92	208–210	213–215[13]
3	3-$NO_2C_6H_4$	Et	O	85	229–230	226–227[13]
4	2-$NO_2C_6H_4$	Et	O	70	205–207	206–208[13]
5	4-$MeOC_6H_4$	Et	O	82	198–200	201–203[13c]
6	2-$MeOC_6H_4$	Et	O	70	260–262	262[13d]
7	4-$NMe_2C_6H_4$	Et	O	80	257–258	256–257[24]
8	$C_6H_5CH{=}CH$	Et	O	70	231–232	232–235[13]
9	2-Furyl	Et	O	95	207–209	209–211[25]
10	n-Bu	Et	O	85	156–158	157–158[26]
11	C_6H_5	Et	S	95	208–209	208–210[13]
12	4-Cl C_6H_4	Et	S	85	191–192	192–195[24]
13	4-$MeOC_6H_4$	Et	S	87	153–156	150–152[13]
14	3-$NO_2C_6H_4$	Et	S	70	203–205	206–207[13]
15	C_6H_5	Me	O	85	229–231	233–236[13]
16	4-Cl C_6H_4	Me	O	85	203–205	204–207[13]
17	4-$MeOC_6H_4$	Me	O	70	189–192	192–194[13]
18	2-Furyl	Me	O	95	208–209	210–212[27]

[a]Products were characterized by their physical constants, comparison with authentic samples, and IR and NMR spectroscopy.
[b]Isolated yield.
[c]Reaction is performed at 110°C.
[d]Reaction is performed at 100°C.

EXPERIMENTAL

Chemicals were purchased from Fluka, Merck, and Aldrich chemical companies. Yields refer to isolated products. Products were characterized by their physical constants, comparison with authentic samples, and IR and NMR spectroscopy. The purity determination of the substrates and reaction monitoring were accompanied by TLC on silica-gel polygram SILG/UV 254 plates.

General Procedure

A mixture of β-dicarbonyl compound (1 mmol), aldehyde (1 mmol), urea or thiourea (1.5 mmol), and $ZrOCl_2 \cdot 8H_2O$ (0.1 mmol) was heated in an oil bath (90°C) for 2 h. After completion (monitored by TLC), the reaction mixture was poured into water (5 mL). The precipitate was filtered and successively washed with water (5 mL) and petroleum ether–EtOAc (5 : 1, 5 mL). The crude product was purified by recrystallization to give the pure products in good to high yields.

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