Aluminium Nitrate Nonahydrate ($Al(NO_3)_3 \cdot 9\ H_2O$): An Efficient Oxidant Catalyst for the One-Pot Synthesis of *Biginelli* Compounds from Benzyl Alcohols

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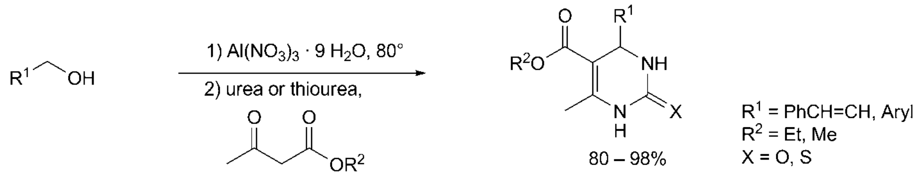
A clean and efficient tandem oxidative cyclocondensation process is reported for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-one or -thione derivatives from primary aryl alcohols, *β*-keto esters, and urea or thiourea in the presence of $Al(NO_3)_3 \cdot 9\ H_2O$ as oxidant catalyst (*Scheme*, *Table 5*).

Introduction. – The *Biginelli* reaction attracts still organic chemists interested in finding milder and more efficient procedures for the synthesis of dihydropyrimidinones [1][2]. At present, several general methods are known for the preparation of dihydropyrimidinones, in the presence of various *Lewis* or protic acids such as [$Cu(OTf)_2$] [3], metal acetate [4], GaI_3 [5], $FeCl_3$ immobilized in Al-MCM 41 [6], melamine trisulfonic acid [7], 4-aminobenzenesulfonic acid [8], nano-$BF_3 \cdot SiO_2$ [9], silica-gel-supported polyphosphoric acid (PPA–SiO_2) [10], alumina/H_2SO_4 [11], dodecylphosphonic acid [12], and 1,3-dichloro-5,5-dimethylhydantoin [13].

Results and Discussion. – Following our work [14–16] on the development of useful and more sustainable synthetic methodologies, and leading with the recent investigations involving oxidation of alcohols and the subsequent trapping of C=O intermediates with appropriate nucleophiles in a one-pot manner [17], we report here our preliminary investigation dealing with the use of $Al(NO_3)_3 \cdot 9\ H_2O$ as an oxidant catalyst to accomplish the *Biginelli* one-pot reaction starting from benzyl alcohols by means of a tandem oxidative process (*Scheme*).

Scheme



At the beginning of this work, we studied the efficiency of $Al(NO_3)_3 \cdot 9\ H_2O$ as an oxidant catalyst in the *Biginelli* reaction by mixing BnOH (1 mmol), ethyl acetoacetate

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(=ethyl 3-oxobutanoate; 1 mmol), urea (1.5 mmol), and $Al(NO_3)_3 \cdot 9\ H_2O$ (1.0 mmol) at 80°, in a one-step-one-pot tandem oxidative cyclocondensation manner, but, unfortunately, no product was observed even after long reaction times. However, when we added ethyl acetoacetate (1 mmol) and urea (1.5 mmol) to a reaction mixture containing BnOH (1 mmol) oxidized by $Al(NO_3)_3 \cdot 9\ H_2O$ (1.0 mmol), the 3,4-dihydropyrimidin-2(1*H*)-one derivative was formed at 80° within 10 min.

Therefore, we decided to accomplish the *Biginelli* reaction in a two-step-one-pot oxidative cyclocondensation. To answer our question 'can other nitrates act the same as or perhaps better than $Al(NO_3)_3 \cdot 9\ H_2O$ in the *Biginelli* oxidative cyclocondensation reactions?', we decided to study first the efficiency of other metal nitrates (1 mmol) in the oxidation of BnOH (1 mmol) as a model substrate under solvent-free condition at 80°. As it can be seen from *Table 1*, the best result was was obtained with $Al(NO_3)_3 \cdot 9\ H_2O$.

Table 1. *Reactivity Trend of Some Metal Nitrates in the Oxidation of BnOH to PhCHO*[a])

Metal nitrate	Time [min]	Yield [%][b])	Metal nitrate	Time [min]	Yield [%][b])
$Al(NO_3)_3$	15	93	$Bi(NO_3)_3$	15	90
$NaNO_3$	240	49	$Zn(NO_3)_2$	60	76
$Ni(NO_3)_2$	90	36	$Cu(NO_3)_2$	100	67

[a]) Reaction conditions: BnOH (1 mmol), metal nitrate (1 mmol), no solvent, 80°. [b]) Yield determined by GC.

Concomitant tests were carried out to optimize the reaction conditions with respect to the reaction media, oxidant amount, and temperature. Comparing the oxidation of BnOH in different solvents including MeCN, EtOH, dioxane, THF, hexane, and H_2O under reflux with the reaction at 70° without solvent showed that the best result was achieved under solvent-free conditions (*Table 2*); the oxidation in solvents gave significantly lower yields and needed longer reaction times.

Table 2. *Oxidation of BnOH to PhCHO in the Presence of $Al(NO_3)_3 \cdot 9\ H_2O$: Comparing Solvent-Free Conditions with Various Solvents*[a])

Solvent	Time [min]	Yield [%][b])	Solvent	Time [min]	Yield [%][b])
–	15	92	EtOH	350	59
H_2O	480	0	THF	210	40
MeCN	150	90	hexane	480	0

[a]) Reaction conditions: BnOH (1 mmol), metal nitrate (1 mmol), 70°. [b]) Yield determined by GC.

In 'linear' synthesis, the overall yield quickly drops with each reaction step. Therefore, optimizing the yield of the oxidation step is very important in the cyclocondensation procedure. To increase the yield of PhCHO, we decided to evaluate the influence of the amount of $Al(NO_3)_3 \cdot 9\ H_2O$ and temperature on the yield of oxidation of BnOH. Increasing the amount of $Al(NO_3)_3 \cdot 9\ H_2O$ from 0.3 to 1.5 mmol led to an increase of yield of PhCHO from 81 to 99% (*Table 3*). Decreasing the temperature from 80° to room temperature reduced the yield of PhCHO from 99 to 37% (*Table 4*).

Table 3. *Influence of the Amount of $Al(NO_3)_3 \cdot 9\ H_2O$ on the Oxidation of BnOH to PhCHO*[a])

$Al(NO_3)_3 \cdot 9\ H_2O$ [mmol]	Yield [%][b])	$Al(NO_3)_3 \cdot 9\ H_2O$ [mmol]	Yield [%][b])
1.5	99	1	93
1.3	98	0.6	86
1.2	98	0.3	81

[a]) Reaction condition: BnOH (1 mmol), 80°, 15 min. [b]) Yield determined by GC.

Table 4. *Influence of Temperature on the Oxidation of Neat BnOH by $Al(NO_3)_3 \cdot 9\ H_2O$*[a])

Temperature [°]	Time [h]	Yield [%][b])	Temperature [°]	Time [h]	Yield [%][b])
80	0.25	99	40	7	62
60	4	79	r.t.	24	37

[a]) 1.5 mmol of $Al(NO_3)_3 \cdot 9\ H_2O$ per mmol of BnOH was used. [b])Yield determined by GC.

Thus, the optimized conditions for the oxidation of 1 mmol of BnOH is as follows: 1.5 mmol of $Al(NO_3)_3 \cdot 9\ H_2O$ at 80° in the absence of solvent.

Next, we added urea and ethyl acetoacetate to the PhCHO obtained from the oxidation of BnOH under optimized conditions. The reaction was completed at 80° within 10 min. After adding cold EtOH to the reaction mixture, almost pure 3,4-dihydropyrimidin-2(1*H*)-one derivative was precipitated in 90% yield, which did not require further purifcation (*Table 5*, *Entry 1*). We also explored the use of functionalized benzyl alcohols carrying either electron-releasing or electron-withdrawing substituents in *meta*- and *para*-position to establish the scope and limitation of the current procedure. The 3-nitro derivative of benzyl alcohol required relatively long reaction times to complete the *Biginelli* reaction (*Table 5*, *Entries 4* and *6*), while BnOH and 4-bromobenzyl alcohol required shorter reaction times (*Entries 1*, *3*, *7* and *11*). The highest yields were found for 4-fluorobenzyl alcohol (*Entries 8* and *9*).

Conclusions. – We developed an efficient catalytic protocol wherein $Al(NO_3)_3 \cdot 9\ H_2O$ was explored as an oxidant catalyst for the sequential oxidation and condensation reaction of alcohols with β-keto esters and urea or thiourea to result in the formation of corresponding 3,4-dihydropyrimidin-2(1*H*)-one or -thione derivatives. The present procedure provides an efficient and improved modification of the *Biginelli* reaction. Mild reaction conditions, ease of workup, simple procedure, good to excellent yields, and a cheap and nontoxic oxidant catalyst are features of this new procedure. Moreover, the method tolerates a wide variety of substituents in all three components.

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Table 5. *Synthesis of 3,4-Dihydropyrimidin-2(1*H*)-one or -thione Derivatives in the Presence of* $Al(NO_3)_3 \cdot 9\,H_2O$ *as Oxidant Catalyst (cf. Scheme)*[a])

Entry	R^1	R^2	X	Time [min]	Yield [%][b])
1	Ph	Et	O	10	90
2	4-MeO–C_6H_4	Et	O	30	80
3	4-Br–C_6H_4	Et	O	20	89
4	3-NO_2–C_6H_4	Et	O	90	80
5	4-MeO–C_6H_4	Me	O	30	80
6	3-NO_2–C_6H_4	Me	O	90	83
7	4-Br–C_6H_4	Me	O	20	92
8	4-F–C_6H_4	Me	O	45	98
9	4-F–C_6H_4	Me	O	30	98
10	Ph	Et	S	15	82
11	4-Br–C_6H_4	Et	S	10	86
12	PhCH=CH	Et	O	120	80

[a]) Reaction conditions: alcohol (1 mmol) and $Al(NO_3)_3 \cdot 9\,H_2O$ (1.5 mmol) at 80°; then urea (1.5 mmol) and β-keto ester (1 mmol) at 80°. [b]) Yield refers to the isolated product. The products were characterized by comparison of their spectroscopic and physical data with those of samples synthesized by reported procedures.

Experimental Part

Typical Procedure: Synthesis of Ethyl 1,2,3,4-Tetrahydro-6-methyl-2-oxo-4-phenylpyrimidine-5-carboxylate (*Table 5*, *Entry 1*). A mixture of BnOH (1 mmol, 108 mg) and $Al(NO_3)_3 \cdot 9\,H_2O$ (1.5 mmol, 562 mg) was heated at 80° for 15 min in a test tube (TLC monitoring). After completion of the oxidation process, ethyl acetoacetate (1 mmol, 105 mg) and urea (1.5 mmol, 90 mg) were added to the mixture, which was heated with stirring at 80°. The reaction was completed within 10 min. After cooling to r.t., 96% EtOH (*ca.* 10 ml) was added under vigorous stirring. The almost pure product was gradually precipitated. The precipitate was filtered, washed with cold EtOH (5 ml), and dried under vacuum; ethyl 1,2,3,4-tetrahydro-6-methyl-2-oxo-4-phenylpyrimidine-5-carboxylate (468 mg, 90%). M.p. 202–204° [18]: 200–202°).

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