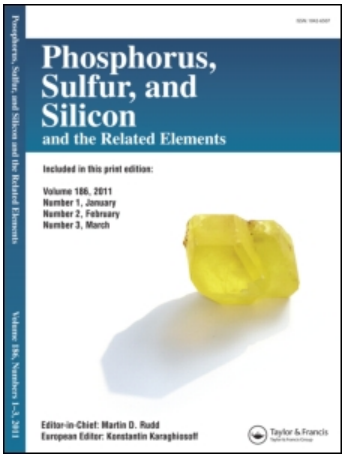

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$FeCl_3 \cdot 6H_2O$-CATALYZED CONVERSION OF ACYLALS TO DIHYDROPYRIMIDINONES UNDER MICROWAVE CONDITIONS: A NEW PROCEDURE FOR THE BIGINELLI REACTION

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$FeCl_3 \cdot 6H_2O$ efficiently catalyzed the three-component condensation reaction of acylals, ethyl acetoacetate, and urea or thiourea to afford the corresponding 3,4-dihydropyrimidin-2(1H)-ones in good yields under solvent-free and microwave conditions.

Keywords Biginelli reaction; dihydropyrimidine; microwave irradiation; solvent-free

INTRODUCTION

Dihydropyrimidinone derivatives have attracted considerable interest in recent years because of their therapeutic and pharmacological properties. For example, they can serve as the integral backbones of several calcium channel blockers,[1] antihypertensive agents,[2] and α-1a-antagonists.[3]

The classical Biginelli reaction of an aldehyde, 1,3-dicarbonyl, and urea or thiourea requires strongly acidic conditions with relatively low yields.[4] In order to improve the efficiency of the Biginelli reaction, many catalysts, such as zirconium (IV) chloride,[5] CuI,[6] silica triflate,[7] chloroacetic acid,[8] $Y(NO_3)_3 \cdot 6H_2O$,[9] heteropoly acids,[10] and so on, have been developed. Some of them are quite fascinating from the synthetic chemist's point of view; however, some drawbacks still remain. For example, some catalysts are expensive, complex, or unavailable, and organic solvents are always used. Furthermore, many heavy metallic salts were used, which resulted in pollution of the environment to some extent.

The utility of microwave irradiation (MW) to carry out organic reactions has now become a regular feature. This is evident from the increasing number of reviews[11] and books[12] published on the use of microwave technology for carrying out organic reactions.

The main benefits of performing reactions under microwave irradiation conditions are the significant rate enhancements and the higher product yields that can be observed.[13] It is clear that the application of microwave technology to rapid synthesis of potential biological molecules on liquid phases or hybrid polymers and solid phases is a useful tool

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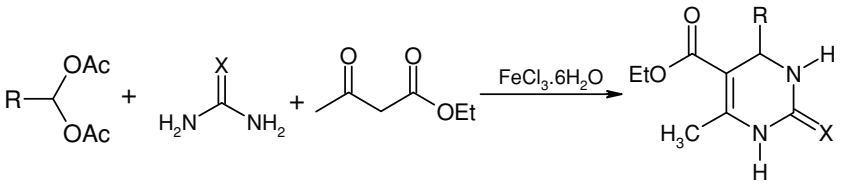
for the combinatorial and/or medicinal community, for whom reaction speed is of great importance.

Acylals (geminal diacetates) are frequently used as protecting groups for aldehydes, which are stable to basic and neutral conditions. In addition, the acylal functionality can be converted into other useful functional groups by reaction with appropriate nucleophiles.[14,15] For example, recently a novel synthesis of chiral allylic esters has been developed using palladium-catalyzed asymmetric allylic alkylation of gem-diesters.[16] The synthesis of homoallyl acetates by allylation of 1,1-diacetates has also been reported.[17]

In continuation of our study on the Biginelli reaction,[18] we focused on the condensation reaction of acylals, ethyl acetoacetate, and urea or thiourea under microwave irradiation and solvent-free conditions (Scheme 1). $FeCl_3{\cdot}6H_2O$ was used as a homogeneous, nonvolatile, cheap, safe, and commercially available catalyst.



Scheme 1

RESULTS AND DISCUSSION

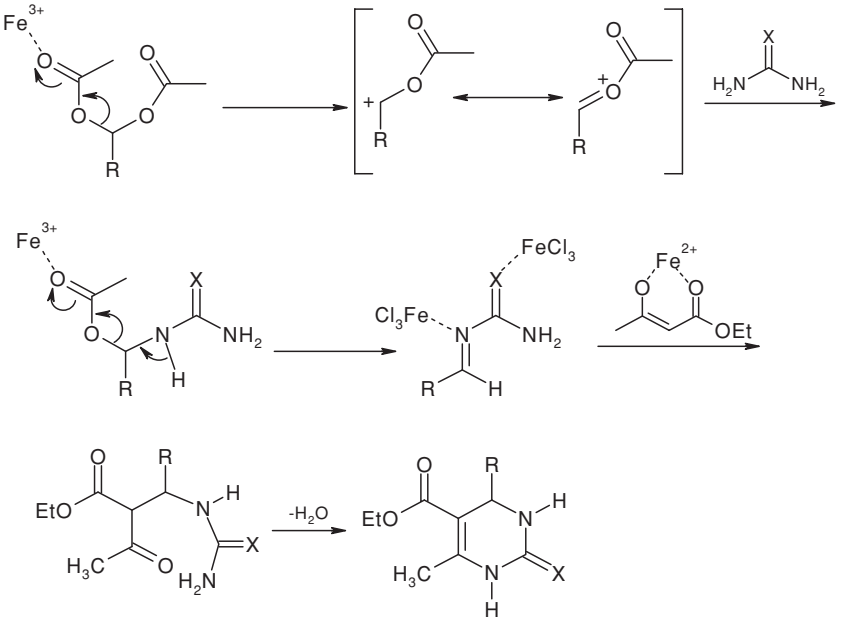
The reaction of benzaldehyde acylal, ethyl acetoacetate, and urea was selected as a model. The best result was achieved by carrying out the reaction with (1:1:1:1.5) mol ratio of $FeCl_3{\cdot}6H_2O$, acylal, ethyl acetoacetate, and urea for 15 min under 180 W microwave irradiation. Using this optimized reaction condition, and then the reactions of various acylals, ethyl acetoacetate and urea or thiourea were investigated. The results are shown in Table I, and all the products were characterized by mp, IR, ^1H, and ^{13}C NMR spectral data.

According to the mechanistic studies reported in the literature,[19] in the first step of the Biginelli reaction, N-acyliminium ion is formed as the key intermediate by the acid-catalyzed condensation of acylal and urea. Interception of this iminium ion by ethyl 3-oxopentanoate, possibly through its enol tautomer, results in the formation of an open-chain

Table I $FeCl_3{\cdot}6H_2O$ catalyzed biginelli reaction using acylals

Entry	Product	R	X	Mp	Yield (%)
1	**4a**	Ph	O	196[18]	85
2	**4b**	4-ClC_6H_4	O	204[18]	92
3	**4c**	2-$CH_3C_6H_4$	O	174[24]	84
4	**4d**	4-$CH_3C_6H_4$	O	205[18]	88
5	**4e**	4-$CH_3OC_6H_4$	O	192[22]	76
6	**4f**	1-Naph	O	250[22]	92
7	**4g**	Ph	S	190[18]	72
8	**4h**	4-ClC_6H_4	S	185[18]	60
9	**4i**	2-$CH_3C_6H_4$	S	175[23]	68
10	**4j**	4-$CH_3C_6H_4$	S	190[18]	68
11	**4k**	4-$CH_3OC_6H_4$	S	145[8]	55

ureide, which then cyclizes to the dihydropyrimidinone derivative (Scheme 2). The success of the Lewis acid–catalyzed method may be the result of specific stabilization of the N-acyliminium ion intermediates.



Scheme 2

EXPERIMENTAL

All reagents were purchased from Merck Chemical Company and were used without further purification. Acylals were prepared according to the methods in the literature.[20,21] IR spectra were recorded on a Mattson 1000 FT-IR spectrometer (KBr). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-500 Avance spectrometer in DMSO-d_6.

Typical Experimental Procedure

Acylal (1 mmol), ethyl acetoacetate (1 mmol), urea (1.5 mmol), and $FeCl_3 \cdot 6H_2O$ (1 mmol) were mixed in a vessel. The resulting mixture was exposed to microwave irradiations in 1 min pulses each at 180 W with 30 sec intervals for cooling. The total period of microwave irradiation was 15 min. After the completion of the reaction, the mixture was dissolved in ethanol and poured into cold water. The precipitate was filtered off, washed with H_2O, and recrystallized from 70% ethanol to afford pure dihydropyrimidinone.

Product Characterization Data of Some 3,4-Dihydropyrimidin-2-(1H)-ones

5-(Ethoxycarbonyl)-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one (4a). ^{1}H NMR (DMSO-d_6): $\delta = 9.18$ (s, 1H, NH), 7.73 (s, 1H, NH), 7.23–7.34 (m, 5H, arom CH), 5.15 (d, $J = 3.2$ Hz, 1H, CH), 3.99 (q, $J = 7.1$ Hz, 2H, CH_2), 2.25 (s, 3H,

CH_3), 1.10 (t, $J = 7.1$ Hz, 3H, CH_3). ^{13}C NMR (DMSO-d_6) $\delta = 166.20$, 152.99, 149.22, 145.73, 129.25, 128.12, 127.11, 100.13, 60.04, 54.83, 18.64, 14.94.

4-(4-Chlorophenyl)-5-(ethoxycarbonyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (4b). ^1H NMR (DMSO-d_6): $\delta = 9.24$ (s, 1H, NH), 7.77 (s, 1H, NH), 7.40 (d, 8.4 Hz, 2H, arom CH), 7.25 (d, $J = 8.4$ Hz, 2H, arom CH), 5.14 (d, $J = 3.3$ Hz, 1H, CH), 3.99 (q, $J = 7.1$ Hz, 2H, CH_2), 2.26 (s, 3H, CH_3), 1.10 (t, $J = 7.1$ Hz, 3H, CH_3). ^{13}C NMR (DMSO-d_6) $\delta = 166.07$, 152.79, 149.60, 144.66, 132.64, 129.26, 129.05, 99.69, 60.12, 54.28, 18.67, 14.94.

5-(Ethoxycarbonyl)-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (4e). ^1H NMR (DMSO-d_6): $\delta = 9.15$ (s, 1H, NH), 7.67 (s, 1H, NH), 7.15 (d, $J = 8.6$ Hz, 2H, arom CH), 6.88 (d, $J = 8.6$ Hz, 2H, arom CH), 5.10 (d, $J = 2.9$ Hz, 1H, CH), 3.99 (q, $J = 7.1$ Hz, 2H, CH_2), 3.72 (s, 3H, CH_3), 2.24 (s, 3H, CH_3), 1.11 (t, $J = 7.1$ Hz, 3H, CH_3). ^{13}C NMR (DMSO-d_6) $\delta = 166.24$, 159.31, 153.02, 148.87, 137.92, 128.26, 114.56, 100.44, 60.01, 55.91, 54.20, 18.62, 14.96.

5-(Ethoxycarbonyl))-6-methyl-4-phenyl-3,4-dihydropyrimidine-2(1H)-thione (4f). ^1H NMR (DMSO-d_6): $\delta = 10.33$ (s, 1H, NH), 9.65 (s, 1H, NH), 7.37–7.22 (m, 5H, arom CH), 5.18 (d, $J = 3.4$ Hz, 1H, CH), 4.02 (q, $J = 7.1$ Hz, 2H, CH_2), 2.30 (s, 3H, CH_3), 1.12 (t, $J = 7.1$ Hz, 3H, CH_3). ^{13}C NMR (DMSO-d_6) $\delta = 175.11$, 165.99, 145.89, 144.37, 129.43, 128.54, 127.25, 101.58, 60.45, 54.91, 18.03, 14.87.

5-(Ethoxycarbonyl)-4-(4-methylphenyl)-6-methyl-3,4-dihydropyrimidine-2(1H)-thione (4i). ^1H NMR (DMSO-d_6): $\delta = 10.30$ (s, 1H, NH), 9.61 (s, 1H, NH), 7.15 (d, $J = 8.0$ Hz, 2H, arom CH), 7.11 (d, $J = 8.0$ Hz, 2H, arom CH), 5.14 (d, $J = 3.0$ Hz, 1H, CH), 4.01 (q, $J = 7.1$ Hz, 2H, CH_2), 2.30 (s, 3H, CH_3), 2.27 (s, 3H, CH_3), 1.11 (t, $J = 7.1$ Hz, 3H, CH_3). ^{13}C NMR (DMSO-d_6) $\delta = 175.03$, 166.01, 145.73, 141.47, 137.76, 129.92, 127.16, 101.70, 60.42, 54.61, 21.53, 18.01, 14.89.

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