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Synthetic Communications

An International Journal for Rapid Communication of Synthetic Organic Chemistry

ISSN: 0039-7911 (Print) 1532-2432 (Online) Journal homepage: https://www.tandfonline.com/loi/lsyc20

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To cite this article: Srinivasa Rao Ambati, Jeevan Lal Patel, Satish Gudala, Komal Chandrakar, Santhosh Penta, S. P. Mahapatra & Subhash Banerjee (2019): Synthesis of novel coumarinyl-pyrido[2,3-*d*]pyrimidine-2,4-diones using task-specific magnetic ionic liquid, [AcMIm]$FeCl_4$ as catalyst, Synthetic Communications, DOI: 10.1080/00397911.2019.1686526

To link to this article: https://doi.org/10.1080/00397911.2019.1686526

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https://doi.org/10.1080/00397911.2019.1686526

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Synthesis of novel coumarinyl-pyrido[2,3-*d*]pyrimidine-2,4-diones using task-specific magnetic ionic liquid, [AcMIm]$FeCl_4$ as catalyst

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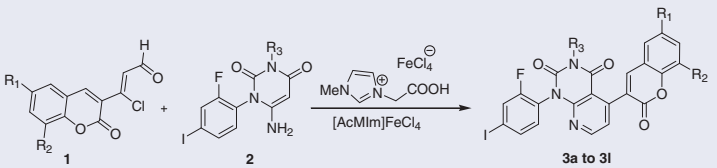
ABSTRACT

An acid-functionalized magnetic ionic liquid, 1-acyl-3-methylimidazolium tetrachloroferrate, [AcMIm]-$FeCl_4$ has been utilized for the synthesis of a series of novel highly functionalized coumarinyl-pyrido[2,3-*d*]pyrimidine-2,4-dione derivatives **(3a–3l)** by the reactions of various 3-chloro-3-(2-oxo-2*H*-chromen-3-yl)acrylaldehydes (**1**) with functionalized aryl, 6-aminouracils. The major significant of the present procedure is the use of task-specific acidic ionic liquid which act as catalyst as well as reaction medium and thus avoiding use of organic solvent and/or protic acid catalyst. The other major advantages of the protocol are (i) shorter reaction time (1 h), (ii) easy work up procedure, (iii) excellent yields of products (91–94%), and (iv) recyclability of catalyst. The compounds **(3a–3l)** were identified using FT-IR, ^{1}H NMR, and ^{13}C NMR and mass spectroscopic studies.

GRAPHICAL ABSTRACT



ARTICLE HISTORY
Received 7 July 2019

KEYWORDS
β-Chloro coumarinyl aldehydes; coumarinyl-pyrido[2,3-d]pyrimidine-2,4-diones; environmentally benign synthesis; task-specific acidic ionic liquid

Introduction

Ionic liquids (ILs) have attracted significant interest as environmentally friendly or green reaction media in organic synthesis because of their unique properties, such as non-volatility, non-flammability, low vapor pressure, recyclability, excellent thermal stability, and desirable solvating properties.[1] On the other hand, functionalized task-specific ILs even more attractive due to presence of specific functionality which can initiate a particular reaction. Moreover, many reactions gain acceleration in ILs due to

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stabilization of charged intermediates or ions.[2] As consequences, ILs have been used in many organic reactions—for example, three-component reactions[3] and carbon–carbon bond-forming reactions, such as Michael addition,[4] Henry reaction,[5] Knoevenagel condensation, and Heck reaction.[6] Recently, the discovery and development of transition-metal containing multifunctional ILs have emerged as a progressing area in the field of IL-based research.[7] These materials have showed combined advantages of ILs with the catalytic, spectroscopic, or magnetic[8] properties of metal ions. On the other hand, iron has appeared as a promising and feasible catalyst for various organic transformations because iron is one of the most inexpensive, high solubility in organic solvents, excellent Lewis acidity, and non-pollutant metals on earth.[9] Very recently, few organic transformations with iron-based magnetic ILs (MAILs) as the catalyst or reaction media have been reported. In particular, 1-butyl-3- methylimidazolium tetrachloroferrate ([BMIm]$FeCl_4$) was employed as a catalyst in synthesis of quinazolines, glycolysis of poly(ethylene terephthalate), Friedel–Crafts acylation, aryl-Grignard cross-coupling of alkyl halides, and the dimerization of bicyclohepta-2,5-diene.[10] Recently, we have demonstrated synthesis of and characterization of 1-acyl-3-methylimidazolium tetrachloroferrate, [AcMIm]$FeCl_4$ for the oxidative hydroxylation of aryl boronic acid, and Friedal–Craft acylation reactions.[11]

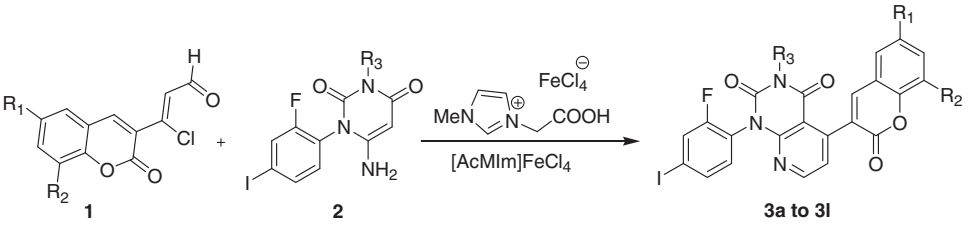
On the other hand, nitrogen-containing heterocyclic molecules have shown a wide spectrum of biological activities and frequently used in the pharmaceutical industries as building blocks to design more potent compounds.[12] Accordingly, pyrido[2,3-*d*]pyrimidine scaffold, an important structural motif, present in a number of compounds showing a variety of biological properties, such as anticancer, antitumor, antimicrobial, growth regulators, antipyretic, analgesic, antihistaminic, PDE4 inhibitors, adenosine kinase inhibitor, and tyrosine kinase inhibitor[13] activities. On the other side, coumarin (2*H*-1-benzopyran-2-one) and its derivatives attracted much attention due to their diverse pharmaceutical properties such as anti-HIV, anticancer, anti-influenza, antialzheimer, antituberculosis, antiviral, and antimicrobial activities.[14]

Surveying literature revealed that a number of approaches to the synthesis of pyrido[2,3-*d*]pyrimidine-2,4-dione derivatives have been reported and are mostly based on the reaction of 6-aminouraciles and suitable bifunctional electrophilic substrates, such as acetylenic ketones and esters, α,β-unsaturated carbonyls and nitriles, 1,3-dicarbonyl compounds, and condensation with aldehydes and active methylenes.[15–18] Among the reported pyrido[2,3-*d*]pyrimidine-2,4-diones, synthesis of 3-cyclopropyl derivatives is highly limited.

Results and discussions

As a part of our continuing interest to synthesize biologically active heterocycles[19] and in developing task-specific ILs,[20] herein, we report the synthesis of highly functionalized coumarinyl-pyrido[2,3-*d*]pyrimidine-2,4-dione derivatives using a [AcMIm]$FeCl_4$, under organic solvent/acids/base/or ligand-free reaction conditions (Scheme 1).

The key intermediates 3-chloro-3-(2-oxo-2*H*-chromen-3-yl)acrylaldehyde (1) and functionalized aryl, 6-aminouracils (2) were prepared according to the reported method.[21] In our initial studies, 3-chloro-3-(2-oxo-2*H*-chromen-3-yl)acrylaldehyde (1a)



Compound	R_1	R_2	R_3
3a	H	H	Cyclo propyl
3b	Br	H	Cyclo propyl
3c	Br	Br	Cyclo propyl
3d	OMe	H	Cyclo propyl
3e	Cl	H	Cyclo propyl
3f	Cl	Cl	Cyclo propyl
3g	H	H	Methyl
3h	Br	H	Methyl
3i	Br	Br	Methyl
3j	OMe	H	Methyl
3k	Cl	H	Methyl
3l	Cl	Cl	Methyl

Scheme 1. Synthesis of coumarinyl pyrido[2,3-*d*]pyrimidine-2,4-dione derivatives using magnetic ionic liquid, [AcMIm]$FeCl_4$.

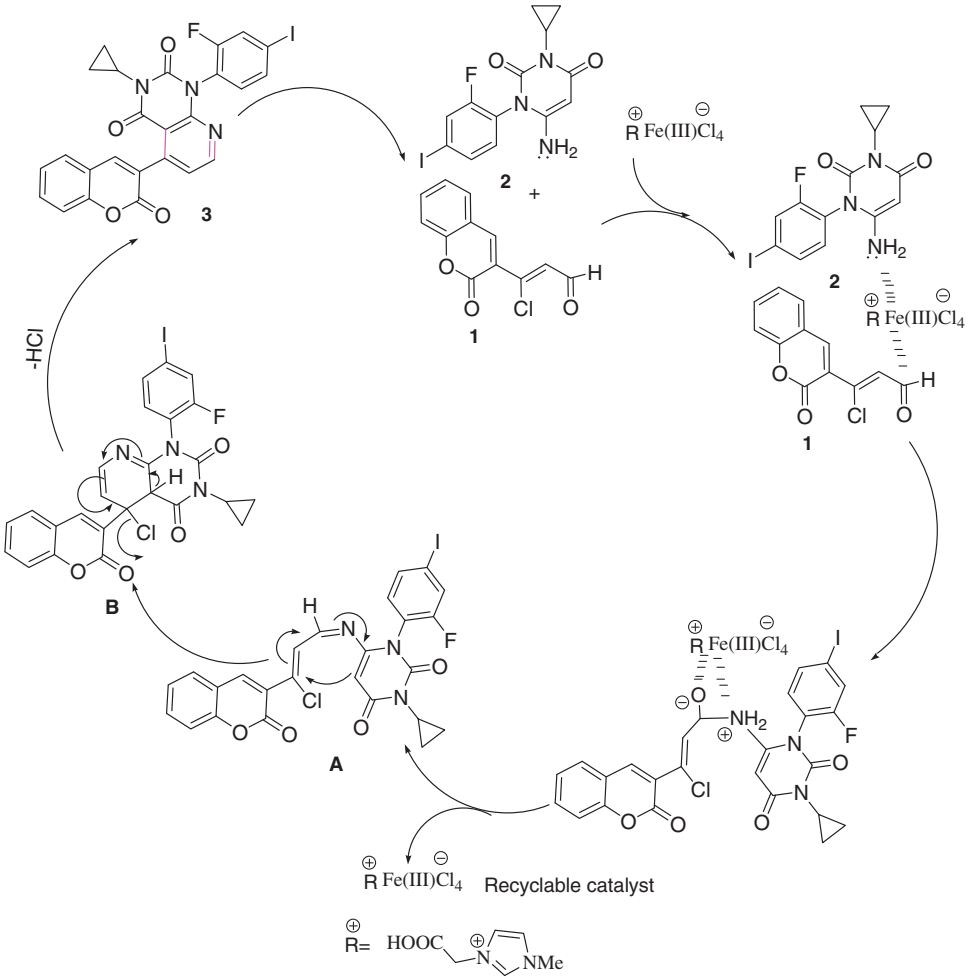
Table 1. Optimization of reaction conditions for the synthesis of title compounds.

Entry	Solvent/catalyst[a]	Temperature (°C)	Time (h)	Yields (%)[b]
1	Acetic acid	Reflux	7.0	35
2	Trifluoro acetic acid	Reflux	7.0	60
3	Ethanol	Reflux	7.0	Trace
4	CH_3CN	Reflux	7.0	Trace
5	DMF	Reflux	7.0	Trace
6	[AcMIm]Cl (20 mol %)	80 °C	1.0	65
7	$C_2H_5OH/FeCl_3$ (1 mol %)	RT	7.0	5
8	$C_2H_5OH/FeCl_3$ (1 mol %)	Reflux	7.0	12
9	$C_2H_5OH/FeCl_3$ (5 mol %)	Reflux	7.0	20
10	$CH_3CN/FeCl_3$ (5 mol %)	Reflux	7.0	35
11	$CH_3CN/FeCl_3$ (10 mol %)	Reflux	7.0	35
12	Dioxane/$FeCl_3$ (5 mol %)	Reflux	7.0	15
13	[AcMIm]$FeCl_4$ (10 mol %)	RT	1.0	70
14	[AcMIm]$FeCl_4$ (20 mol %)	RT	1.5	75
15	[AcMIm]$FeCl_4$ (20 mol %)	60 °C	1.0	94
16	[AcMIm]$FeCl_4$ (30 mol %)	80 °C	1.0	94

[a]Reagents and conditions: 1 (1.0 mmol), 2 (1.0 mmol), [AcMIm]$FeCl_4$ (20 mol %, 67 mg), or organic solvents (2 mL), [b]Isolated yields. All reactions were monitored with TLC.

with 6-amino-3-cyclopropyl-1-(2-fluoro-4-iodo-phenyl)-1*H*-pyrimidine-2,4-dione (2a) and solvents/ionic liquids were used as a model substrates to optimize the reaction conditions. As shown in Table 1, the [AcMIm]$FeCl_4$ played an important role on the yield of products. The reaction gave the highest yield (94%) at 60 °C in the presence of 20 mol % of [AcMIm]$FeCl_4$ (Table 1, entry 15).

Increasing the amount of [AcMIm]$FeCl_4$ to 30 mol % and temperature, however, the yield of **3a** did not improve to a great extent (Table 1, entry 16). Other acidic solvents/catalysts such as AcOH and TFA were also used to compare the reaction yields. In these



Scheme 2. The plausible mechanism for the synthesis of coumarinyl-pyrido[2,3-]pyrimidine-2,4-dione derivatives.

cases, the products were isolated in poor yields (Table 1, entries 1 and 2). In ethanol, CH_3CN and DMF only a trace amount of 3a was obtained (Table 1, entries 3–5). The reaction also initiated with [AcMIm]Cl and provided 65% of yield (entry 6, Table 1). Since, iron salts are inexpensive, environmentally friendly and acting as a Lewis acid property, the feasibility on $FeCl_3$ alone catalyzed reaction was then examined. A range of solvents and amount of Iron chloride were applied (Table 1, entry 7–12). Only 35% isolated yield of desired product 3a was obtained when 5 mol % of $FeCl_3/CH_3CN$ was employed (Table 1, entry 10).

However, screening of various solvents and catalysts revealed that 20 mol % of [AcMIm]$FeCl_4$ provided the best result in terms of product yield (94%) and reaction time (60 min). Thus, 20 mol % (67 mg) of [AcMIm]$FeCl_4$ was chosen as a quantitative catalyst as well as reaction medium to drive the reaction forward with maximum yield of the product. Next, using optimum reaction conditions, we have synthesized series of coumarinyl-pyrido[2,3-*d*]pyrimidine-2,4-dione derivatives **(3a–l)**. The formation of

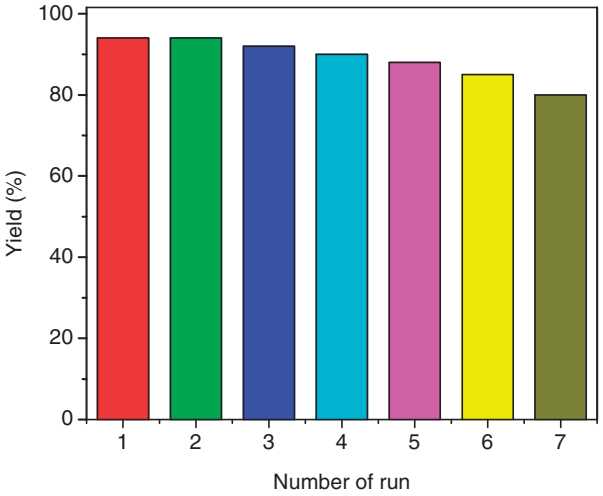


Figure 1. Reusability of [AcMIm]$FeCl_4$ for the synthesis of **3a**.

desired products was confirmed from their analytical and spectral data. For example, the FT-IR spectrum of compound 4a showed three strong absorption peaks at 1724.28, 1653.19, and 1250.02 cm^{-1} for lactone carbonyl, C=N, and aryl ethers, respectively. The ^1H NMR spectrum of compound 4a showed multiplets from $\delta = 0.76–1.08$ for methylene groups of cycloprapane moiety. Two doublets were observed at $\delta = 8.22$ and $\delta = 8.53$ for pyridine ring protons. All the newly synthesized products were identified by the spectroscopic data (**3a–l**). The proposed mechanism is outlined in Scheme 2. In the first step, the carbonyl group and amine group are activated by ([AcMIm]$FeCl_4$, for a condensation reaction between 3-chloro-3-(2-oxo-2*H*-chromen-3-yl)acrylaldehyde 1, and a 6-aminouracils 2 would give the imine intermediate A. This intermediate A, which subsequently undergoes Michael type of reaction with itself *via* dehydrohalogination followed by cylization afforded the desired compound 3.

After the completion of reaction, diethyl ether was added to the reaction mixture to dissolve the organic products and IL was separated using external magnet, washed with ether, dried in vacuum, and reused for subsequent reactions. The recyclability of [AcMIm]$FeCl_4$ was investigated for the synthesis of compound **3a** as model reaction and it was observed the IL remained active up to seven runs (Fig. 1). The little loss in yield could possibly due to the loss of IL and absorption of moisture during recycling process.

Conclusions

A task-specific acid-functionalized magnetic IL, [AcMIm]$FeCl_4$, has been successfully employed as an efficient, inexpensive, magnetically separable catalyst and reaction media for the synthesis of coumarinyl-pyrido[2,3-*d*]pyrimidine-2,4-dione derivatives. The reactions were very clean, high yielding (91–94%) and complete within very short time periods (1 h). The IL was reused at least for seven times without significant loss in catalytic efficacy and stability. To the best of our knowledge this the first example of use of [AcMIm]$FeCl_4$ in one-pot synthesis of nitrogen-containing heterocyclic compounds, and we believe that this finding will open up a new frontier in sustainable organic synthesis.

Experimental

General

All the reagents and solvents were pure, purchased from commercial sources and were used without further purification unless otherwise stated. Melting points were determined in open capillaries with a "Cintex" melting point apparatus (Mumbai, India) and were uncorrected. CHNS analysis was carried out using Carlo Erba EA 1108 automatic elemental analyzer. The purity of the compounds was checked using TLC plates (E.Merck Mumbai, India). IR spectra (KBr) were recorded on a Thermo Nicolet Nexus 670 spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker WM-400 spectrometer in δ ppm using TMS as standard. Mass spectra (EI-MS) were determined on Perkin Elmer (SCIEX API-2000, ESI) at 12.5 eV.

General procedure for the synthesis of coumarinyl-pyrido[2,3-d]pyrimidine-2,4-dione derivatives using acidic, magnetic ionic liquid: (3a–3l)

In a typical experimental procedure, chloroacrylaldehydes (1 mmol) and various 6-amino uraciles (1 mmol) were taken in a magnetic acidic ionic liquid, [AcMIM]$FeCl_4$ (20 mol %, 67 mg). The reaction solution was allowed to stir at 60 °C temperature until completion of the reaction. The reactions were monitored using TLC. After the reaction, final derivatives were easily extracted by washing the ionic liquid layer with diethyl ether (5 × 5 mL) using external magnetic field. The combined organic layer was dried over anhydrous sodium sulfate and evaporated using rotavapor to get the desired products. The crude product was purified by recrystallization from absolute ethanol.

3-Cyclopropyl-1-(2-fluoro-4-iodophenyl)-5-(2-oxo-2H-chromen-3-yl)pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione: (3a)

Yield (94%); mp: 246–250°C; IR (KBr, cm^{-1}), 1724.28 and 1653.19 (C=O), 1491.21 (C=C), 1353 (C–F), 1250.02 (aryl ethers, C–O–C); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 0.76–1.08 (m, 4H, $-CH_2$), 2.77–2.79 (m,1H, –CH), 7.40–7.48 (m, 3H, Ar-H), 7.58 (d, $J = 7.6$ Hz, 1H, Ar-H), 7.69–7.73 (m, 1H, Ar-H), 7.84 (d, $J = 8.4$ Hz, 1H, Ar-H) , 8.02 (d, $J = 9.2$ Hz, 1H, Ar-H), 8.12 (s, 1H, C-4 of coumarin), 8.23 (d, $J = 8.0$ Hz, 1H, pyridine-H) , 8.53 (d, $J = 8.0$ Hz, 1H, pyridine-H). ^{13}C NMR (DMSO-d_6, δ ppm): δ 8.10–8.29, 24.11, 96.96 (d, $^{3}J_{CF} = 9$), 111.23, 114.53, 121.41, 122.09 (d, $^{3}J_{CF} = 18$), 122.95, 124.29, 125.70 (d, $^{2}J_{CF} = 49$), 127.28, 129.28, 130.045 (d, $^{2}J_{CF} = 25$), 133.23, 134.49, 134.63, 146.10, 147.05, 148.36, 149.37, 150.31, 152.45 (d, $^{1}J_{CF} = 269$), 156.35, 159.72, 162.52, 163.37.ESI-MS: 568 [M + H]. *Anal.* Calcd for $C_{25}H_{15}FIN_3O_4$: C,52.93; H, 2.67; N, 7.41; Found: C, 52.87; H, 2.79; N, 7.47.

Full experimental detail, ^{1}H NMR, ^{13}C NMR, and Mass spectral copies. This material can be found via the "Supplementary Content" section of this article's webpage.'

Acknowledgments

The authors are thankful to the Director, NIT Raipur for providing facilities. S. A. thanks the Head, MSN, R&D center for encouragement and valuable suggestions.

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