Lithium Fluoride: Efficient and Recyclable Catalyst for High-Yield Synthesis of Novel 5-Isopropoxycarbonyl-4-Aryl-6-Methyl-3, 4-Dihydropyrimidin-2(1H)-Thiones

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Abstract - **Lithium Fluoride is an efficient, inexpensive and readily available catalyst for the three component, one-pot condensation reaction of an aldehyde, isopropyl acetoacetate and thiourea in ethanol to afford the corresponding dihydropyrimidinones in high yield. The catalyst exhibited remarkable reusable activity. The compounds have been characterized on the basis of their elemental analysis and FT-IR, ^{1}H and ^{13}C NMR spectroscopies.**

Keywords: 3,4-dihydropyrimidin-2(1H)-thiones, Lithium fluoride, One-pot synthesis, Cyclo-condensation, Biginelli reaction

I. Introduction

Biginelli reactions are simple one-pot but low-yielding condensations of 2-dicarbonyl compounds with aldehydes and urea or thiourea in the presence of catalytic amount of acid to produce 3,4-dihydropyrimidin-2(1*H*)-ones[1]. In recent years, interest in this reaction has increased rapidly and several modified procedures aimed at improving the efficiency of the Biginelli dihydropyrimidine synthesis have been reported. For example, modifications and improvements using Lewis acids such as $BF_3.OEt_2$[2], $LaCl_3$[3], $La(OTf)_3$[4], $InCl_3$[5], $InBr_3$[6], $ZrCl_4$[7], $Mn(OAC)_3$[8], $LiClO_4$[9], $Cu(OTf)_2$[10], LiBr[11], TMGT[12] etc., have been reported. However, some of these procedures involve difficulties such as the use of stoichiometric amounts of catalysis, high temperatures, the use of metal halides as catalysts, expensive catalysts, the separation of the product from the catalyst, etc. Moreover, the recovery and reuse of catalysis in any such process offers advantages in terms of a clean and environmentally benign process. We wish to report here a simple but effective procedure for Biginelli's three-component cyclo-condensation producing high yields of 3,4-dihydropyrimidin-2(1*H*)-thiones **4a-g** by employing LiF as a reusable catalyst (Scheme 1).

II. Experimental

Melting points are determined in open capillaries and are uncorrected. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AMX-400 spectrometer operating at 400 and 100.6 MHz respectively. IR spectra were recorded on an AVATAR-330 FT-IR spectrometer in KBr pellets. Elemental analyzes were performed on an Elementar Vario El III analyzer.

A. Preparation of DHPMs

A mixture of aldehyde (10 mmol), isopropyl acetoacetate (10 mmol), thiourea (15 mmol), LiF (1 mmol, 10 mol%) and EtOH (20 ml), was heated at 50^{0}C for 10 to 20 min. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature and poured into crushed ice. The crude product containing also the catalyst was collected on a Buchner funnel by filtration. The mixture of the product and the catalyst was digested in methanol (40 ml). The undissolved catalyst was removed by filtration. The crude product was obtained by evaporation of methanol and further purified by recrystallization from hot ethanol to afford pure dihydropyrimidin-2(1*H*)-thiones. The catalyst could be reused in the next run. All the products were characterized by IR, ^{1}H NMR and ^{13}C NMR spectra.

III. Results and discussion

A. Synthesis

The model reaction of benzaldehyde (10 mmol), isopropyl acetoacetate (10 mmol), thiourea (15 mmol) and LiF (1 mmol, 10 mol%) in EtOH (20 ml) was heated at 50^{0}C for 10 min. gave the product in 96% yield (Scheme 1). The reusability of the catalyst was next checked by the same model reaction eight times. The results are summarized in Table I. It is seen that the efficiency of the catalyst is not reduced on reuse.

Table I. Yields Of 5-Isopropoxycarbonyl-6-Methyl-4-Phenyl-3,4-Dihydropyrimidin- 2(1H)-Thione 4a For Successive Runs

Run	Reaction Time (min.)	Catalyst (in mol%)	Yield (%)	m.p. (^{0} C)
1	10	10	96	201-202
2	10	10	96	202-203
3	10	10	96	202-203
4	10	10	96	201-202
5	10	10	96	201-202
6	10	10	94	202-203
7	10	10	96	202-203
8	10	10	96	201-203

Elemental analysis has been done for all these compounds. The physical data are given in Table II. It is seen that the reaction proceeds with high yields in all cases.

Table II Physical Data For Compounds 4a-g

Entry	R	Time (min.)	Yield (%)	m.p. (^{0} C)
1	H	10	96	201-202
2	4-CH_3	10	96	250-251
3	4-OCH_3	10	98	195-196
4	4-NO_2	20	94	256-257
5	4-F	10	96	239-240
6	4-Cl	10	98	258-259
7	2-Cl	10	92	245-246

Another important feature of this procedure is the survival of a variety of functional groups such as nitro, halides, methyl, methoxy etc., under the reaction conditions. The advantage of the LiF for this reaction lies in its simplicity. This method utilizes readily available reagents at low cost and also affords high yields of DHPMs in short reaction times.

We also studied the LiF promoted Biginelli condensation of benzaldehyde, isopropyl acetoacetate and thiourea in the presence of various solvents, such as acetonitrile, methanol and ethanol. These results are presented in Table III. Among the solvents used for the transformation, ethanol was found to be the best.

Table III Effect Of Various Solvents[a]

Entry	Solvent	Reaction Time (min.)	Yield (%)
1	Acetonitrile	240	58
2	Methanol	60	82
3	Ethanol	10	96

[a]Reaction conditions: aldehyde (10 mmol), isopropyl acetoacetate (10 mmol), thiourea (15 mmol), LiF (1 mmol, 10 mol%) solvent 20 ml under reaction condition.

B. Analysis of Spectra

The compounds were characterized by using IR, ^{1}H NMR and ^{13}C NMR spectra. For **4a** the NMR signals were assigned unambiguously using HMBC and HSQC spectra.

The numbering of atoms in the heterocyclic and aromatic rings is shown in Fig. 1. The protons are numbered accordingly. Thus, the proton at C-4 is denoted as H-4. The protons on the nitrogen atoms N-1 and N-3 are denoted as H-1 and H-3, respectively.

1. I R Spectra

In all cases two separate sharp bands were observed for the two different NH-stretching vibrations. One band was observed in the range 3285-3229 cm^{-1}. The other band was observed in the range 3198-3119 cm^{-1}. The ester carbonyl stretching frequency was observed in the range 1671-1651 cm^{-1}. In compounds **4a-g** the C=S stretching frequency was observed in the range 1599-1581 cm^{-1}.

2. ^{1}H NMR Spectra

In all cases the benzylic proton appeared as a doublet with a J value of 4 Hz. This is due to the coupling between H-4 and H-3.

In the ^{1}H NMR spectrum of **4a** there was a singlet at d 9.94 ppm, which could be attributed to H-1. There was a singlet at d 9.36 ppm, which could be attributed to H-3. The aromatic protons appeared as a multiplet in the range 7.36-7.25 ppm. There was a doublet at d 5.30 ppm, with a J value of 4 Hz, due to the benzylic proton H□4. There was a multiplet at d 4.92 ppm, corresponding to one proton, due to the methine proton of the isopropyl group. There was a singlet at d 2.35 ppm, corresponding to three protons, due to the methyl protons at C-6. There were two doublets at d 1.21 and 1.05 ppm, each corresponding to three protons, due to the two diastereotopic methyl protons of the isopropyl group.

The ^{1}H NMR spectra of **4b-g** were similar to that of **4a** except for the aromatic protons. The signals were assigned by comparing with **4a**. The signals for the aromatic protons were assigned based on known substituent effects[13].

3. ^{13}C NMR spectra

The observed ^{13}C chemical shifts (d, ppm) of **4a** are as follows: 174.10 (C=S), 164.72 (carbonyl carbon of the ester), 144.32 (C-6), 143.30 (C-1'), 128.34 (C-3'), C-5'), 127.13 (C-4'), 126.68 (C-2', C-6'), 101.57 (C-5'), 66.72 (CH carbon of the isopropyl group), 54.53 (C-4), 21.52 and 21.33 (CH_3 carbon of the isopropyl group), 17.45 (CH_3 carbon at C-6). All these assignments were made unambiguously

based on the observed correlations in the HMBC and HSQC spectra. ^{13}C NMR spectra of **4b-g** were similar to that of **4a** except for the aromatic carbons. The signals were assigned by comparing with **4a** and based on known effects of the aromatic substituents[14].

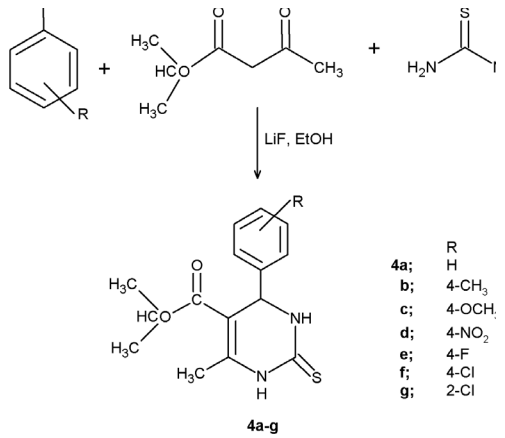
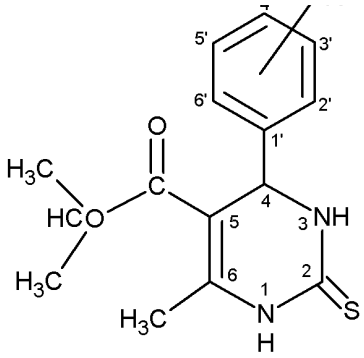


Fig. 1 Target compound numbering



Scheme 1 Synthesis of 5-acetyl-4-aryl-6methyl-3, 4-dihydropyrimidin-2(1-H)-thiones in the absence of catalyst

IV. Characterization of Dhpms

A. 5-Isopropoxycarbonyl-4-(4'-methylphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-thione 4b

IR (KBr) (cm^{-1}): 3285 ad 3183 (N-H str.), 1655 (C=O str.), 1595 (C=S str.); ^1H NMR (DMSO-d_6) (d, ppm): 10.15 (s, 1H, H-1), 9.62 (s, 1H,H-3), 7.18 (d, 2H, J=8 Hz, Ar-H), 7.06 (d, 2H, J = 8 Hz, Ar-H), 5.27 (d, 1H, J = 4Hz, H-4), 4.96 (m, 1H, CH of i-Pr), 2.34 (s, 3H, CH_3 at C-6), 2.28 (s, 3H, CH_3 at C-4'), 1.25 and 1.09 (d, 3H, J = 4 Hz, CH_3 of i-Pr); ^{13}C NMR (DMSO-d_6) (d, ppm): 164.82 (CO of the ester), 174.01 (C-2), 144.23 (C-6), 101.12 (C-5), 66.75 (CH of i-Pr), 53.83 (C-4), 21.64 and 21.42 (CH_3 of i-Pr), 20.83 (CH_3 at C-4'), 17.27 (CH_3 at C-6), 139.89 (C-1'), 126.43 (C-2', C-6'), 128.45 (C-3', C-5'), 136.25 (C-4'). Anal. Calcd for $C_{16}H_{20}N_2O_2S$: C, 63.15; H, 6.57; N, 9.21. Found: C, 63.03; H, 6.59; N, 9.20.

B. 5-Isopropoxycarbonyl-4-(4'-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-thione 4c

IR (KBr) (cm^{-1}): 3232 and 3157 (N-H str.), 1654 (C=O str.), 1595 (C=S str.); ^1H NMR (DMSO-d_6) (d, ppm): 9.54 (s, 1H, H-1), 8.98 (s, 1H, H-3), 7.21 (d, 2H, J = 8 Hz, Ar-H), 6.70 (d, 2H, J = 8 Hz, Ar-H), 5.22 (d, 1H, J = 4 Hz, H-4), 4.98 (m, 1H, CH of i-Pr), 3.75 (s, 3H, OCH_3 at C-4'), 2.29 (s, 3H, CH_3 at C-6), 1.25 and 1.10 (d, 3H, J = 4 Hz, CH_3 of i-Pr); ^{13}C NMR (DMSO-d_6) (d, ppm): 165.81 (CO of the ester), 174.70 (C-2), 144.53 (C-6), 102.14 (C-5), 66.72 (CH of i-Pr), 54.78 (OCH_3 at C-4), 53.74 (C-4), 21.57 and 21.32 (CH_3 of i-Pr), 18.33 (CH_3 at C-6), 135.76 (C-1'), 128.63 (C-2', C-6'), 114.01 (C-3', C-5'), 159.71 (C-4'). Anal. Calcd for $C_{16}H_{20}N_2O_3S$: C, 60.00; H, 6.25; N, 8.75. Found: C, 60.09; H, 6.27; N, 8.73.

C. 5-Isopropoxycarbonyl-4-(4'-nitrophenyl)-6-methyl-3, 4-dihydropyrimidin-2(1H)-thione 4d

IR (KBr) (cm^{-1}): 3257 and 3176 (N-H str.), 1659 (C=O str.), 1598 (C=S str.); ^1H NMR (DMSO-d_6) (d , ppm): 10.32 (s, 1H, H-1), 9.76 (s, 1H, H-3), 8.17 (d, 2H, J = 8 Hz,Ar-H), 7.52 (d, 2H, J = 8 Hz, Ar-H), 5.40 (d, 1H, J = 4 Hz, H-4), 4.99 (m, 1H, CH of i-Pr), 2.34 (s, 3H, CH_3 at C-6), 1.26 and 1.11 (d, 3H, J = 8 Hz, CH_3 of i-Pr); 13C NMR (DMSO-d_6) (d , ppm): 165.35 (CO of the ester), 175.82 (C-2), 147.84 (C-6), 102.19 (C-5), 67.42 (CH of i-Pr), 54.65 (C-4), 22.1 and 21.66 (CH_3 of I-Pr), 18.79 (CH_3 at C-6), 146.42 (C-1'), 128.23 (C-2', C-6'), 124.05 (C-3', C-5'), 150.72 (C-4'). Anal. Calcd for $C_{15}H_{17}N_3O_4S$: C, 53.73; H, 5.07; N, 8.35. Found: C, 53.65; H, 5.09; N, 8.34.

D. 5-Isopropoxycarbonyl-4-(4'-fluorophenyl)-6-methyl-3, 4-dihydropyrimidin-2(1H)-thione 4e

IR (KBr) (cm^{-1}): 3230 and 3195 (N-H str.), 1668 (C=O str.), 1597 (C=S str.); 1H NMR (DMSO-d_6) (d, ppm): 9.94 (s, ^1H, H-1), 9.45 (s, 1H, H-3), 7.21 (d, 2H, J = 8 Hz, Ar-H), 6.92 (d, 2H, J = 8 Hz, Ar-H), 5.28 (d, 1H, J = 4 Hz, H-4), 4.98 (m, 1H, CH of i-Pr), 2.27 (s, 3H, CH_3 at C-6), 1.25 and 1.09 (d, 3H, J = 4 Hz, CH_3 of i-Pr); ^{13}C NMR (DMSO-d_6) (d, ppm): 165.84 (CO of the ester), 174.92 (C-2), 145.38 (C-6), 102.69 (C-5), 66.55 (CH of i-Pr), 54.94 (C-4), 21.57 and 21.28 (CH_3 of I-Pr), 18.53 (CH_3 at C-6), 139.64 (C-1'), 129.54 (C-2' C-6'), 115.43 (C-3', C-5'), 162.68 (C-4'). Anal. Calcd for $C_{15}H_{17}N_2O,SF$: C, 58.63; H, 5.53; N, 9.12. Found: C, 58.56; H, 5.51; N, 9.14.

E. 5-Isopropoxycarbonyl-4-(4'-chlorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-thione 4f

IR (KBr) (cm^{-1}): 3230 and 3117 (N-H str.), 1659 (C=O str.), 1595 (C=S str.); 1H NMR (DMSO-d6) (d, ppm): 10.24 (s, 1H, H-1), 9.66 (s, 1H, H-3), 7.92 (d, 2H, J = 8 Hz, Ar-H), 7.26 (d, 2H, J = 8 Hz, Ar-H), 5.32 (d, 1H, J = 4 Hz, H-4), 4.95 (m, 1H, CH of i-Pr), 2.38 (s, 3H, CH_3 at C-6), 1.21 and 1.08 (d, 3H, J = 4 Hz, CH_3 of i-Pr); ^{13}C NMR (DMSo-d_6) (d, ppm): 164.54 (CO of the ester), 174.27 (C-2), 144.64 (C-6), 101.23 (C-5), 66.92 (CH of i-Pr), 53.78 (C-4), 21.59 and 21.24 (CH_3 of i-Pr), 17.33 (CH_3 at C-6), 142.44 (C-1'), 128.12 (C-2', C-6'), 128.08 (C-3', C-5), 132.54 (C-4). Anal. Calcd for $C_{15}H_{17}N_2O_2SCl$: C, 55.46; H, 5.23; N, 8.62. Found: C, 55.40; H, 5.25; N, 8.61.

F. 5-Isopropoxycarbonyl-4-(2'-chlorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-thione 4g

IR (KBr) (cm^{-1}): 3232 and 3172 (N-H str.), 1662 (C=O str.), 1581 (C=S str.); 1H NMR (DMSO-d_6) (d, ppm): 10.12 (s, 1H, H-1), 8.74 (s, 1H, H-3), 7.32-7.09 (m, 4H, Ar-H), 5.87 (d, 1H, J = 4 Hz, H-4), 4.94 (m, 1H, CH of i-Pr), 2.35 (s, 3H, CH_3 at C-6), 1.20 and 0.83 (d, 2H, J = 4 Hz, CH_3 of i-Pr); ^{13}C NMR (DMSO-d_6) (d, ppm): 165.64 (CO of the ester), 175.05 (C-2), 145.63 (C-6), 101.14 (C-5), 66.48 (CH of i-Pr), 52.72 (C-4), 22.19 and 21.38 (CH_3 of i-Pr), 18.34 (CH_3 at C-6), 139.75 (C-1'), 132.73 (C-2'), 130.36 (C-3', 130.65 (C-4'), 128.48 (C-5'), 129.49 (C-6'). Anal. Calcd for $C_{15}H_{17}N_2O_2SCl$: C, 55.46; H, 5.23; N, 8.62. Found: C, 55.39; H, 5.21; N, 8.64.

V. Conclusion

In summary, this report discloses a new and simple modification of the Biginelli dihydropyrimidinones synthesis. By using LiF_2 as a catalyst, the yields of the one-pot Biginelli reaction can be increased from 20 to 50% to 96-98% while the reaction time was shortened from 18 to 48 h to 10 min. In addition the catalyst can be easily recovered and reused. It not only led to economical automation but also reduces hazardous pollution to achieve environmentally friendly processes. This LiF_2 catalytic one-pot synthesis of dihydropyrimidinones therefore is a simple, high yielding, time saving and environmentally friendly process.

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References

[1] (a) P. Biginelli, Gazz. Chim. Ital. Vol. 23, pp. 360, 1893, (b) C.O. Kappe, Tetrahedron, Vol. 49, pp. 6937, 1993. (c) C.O. Kappe, Acc. *Chem. Res.,* Vol. 33, pp.879-888, 2000.

[2] E.H. Hu, D.R. Sidler, and U.H. Dolling, *J. Org. Chem.,* Vol.63, pp. 3454, 1998.

[3] J. Lu, Y.Bai, Z. Wang, B.Yang, and H. Ma, *Tetrahedron Lett.,* Vol. 41, pp. 9075, 2000.

[4] Y.Ma, C. Qian, L.Wang, and M. Yang, M. *J. Org. Chem.,* Vol. 65, pp. 3864, 2000.

[5] B.C. Ranu, A. Hajra, and U. Jana, *J. Org. Chem.,* Vol. 65, pp. 6270, 2000.

[6] N.Y. Fu, Y.F. Yuan, Z. Cao, S.W. Wang, and J.T. Wang, and C. Peppe, *Tetrahedron,* Vol.58, pp. 4801, 2002.

[7] C.V.Reddy, M. Mahesh, P.V.K. Raju, T.R. Babu, and V.V.N. Reddy, T*etrahedron Lett.,* Vol. 43, pp. 2657, 2002,

[8] K.A. Kumar, M. Kasthuraiah, C.S. Reddy, and C.D. Reddy, *Tetrahedron Lett.,* Vol.42, pp. 7873, 2001.

[9] J.S. Yadav, B.V.S. Reddy, R. Srinivas, C. Venugopal, and T. Ramalingam, Synthesis, pp. 1341, 2001.

[10] A.S. Paraskar, G.K. Dewkar, and A. Sudalai, *Tetrahedron Lett,,* Vol. 44, pp. 3305, 2003.

[11] P.B. Partha, G. Sunil, P. Dipak, P and S.S. Jagir, *Chem. Lett.,* Vol. 10, pp.1038, 2002.

[12] A. Shaabani, and A. Rahmati, Catalysis Lett.,Vol. 100, pp. 177, 2003.

[13] R.M. Silverstein and F.X. Webster, *Spectrometric identification of organic compounds,* 6th Edn. Wiley, New York, pp. 209, 1998.

[14] R.M. Silverstein and F.X. Webster, *Spectrometric identification of organic compounds,* 6th Edn. Wiley, New York, pp. 229, 1998.