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One-pot synthesis of difluoromethyl-containing dihydropyrimidinones catalyzed by $Yb(PFO)_3$ under solvent and dehydrating agent free conditions

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ABSTRACT

The difluoromethyl-containing Biginelli dihydropyrimidinone derivatives were synthesized by a one-pot cyclocondensation of ethyl 4,4-difluoroacetoacetate, urea, and a variety of aldehydes in the presence of 5 mol% ytterbium perfluorooctanoate [$Yb(PFO)_3$] under solvent and dehydrating agent free conditions. The comparison of reaction conditions and products was made among the different 1,3-dicarbonyl substrates (ethyl acetoacetate, ethyl 4,4-difluoroacetoacetate and ethyl 4,4,4-trifluoroacetoacetate) for the Biginelli reaction.

1. Introduction

Organofluorine compounds have received remarkable interest due to their various important applications in many areas, including medicinal, agricultural and materials chemistry [1]. Recently, introduction of a *gem*-difluoromethyl group to bioactive compounds is increasingly used as a strategy to alter properties of molecules for improvement of their biological activity [2]. However, only a limited number of methods are available for the synthesis of *gem*-difluoromethyl-containing compounds compared to their CF_3 analogues. In addition, ethyl 4,4-difluoroacetoacetate is a commercially available difluorinated building block, which can be used to prepare a variety of difluoromethyl-containing compounds [3]. But little is known about the reactivity, properties and products of this difluoro-containing building block when it is used as a component in the multicomponent reactions. There are only a few reports on the three-component reactions involving ethyl difluoroacetoacetate [4].

Dihydropyrimidinone (DHPM) derivatives are widely used as core unit of some biologically active compounds such as calcium channel blockers, anti-tumor agents, and anti-inflammatory drugs [5]. They are generally synthesized by the Biginelli reaction which involves the one-pot condensation of aldehyde, β-ketoester and urea in presence of acidic catalysts [6]. Since the first report on the synthesis of DHPMs by Biginelli in 1893, numerous methods have been reported for the improvement of Biginelli reaction conditions [7]. For example, the use of various Lewis acids such as $BF_3{\cdot}OEt_2$, $FeCl_3$, $LaCl_3$, $Yb(OTf)_3$ (OTf = trifluoromethanesulfonate, the same as below), $La(OTf)_3$, $In(OTf)_3$, $Cu(OTf)_3$, $InCl_3$, $ZrCl_4$, $BiCl_3$, $Mn(OAc)_3$, $LiClO_4$, VCl_3 have been reported [8]. Other new methodologies of organic synthesis, for instance, microwave-assisted synthesis, ultrasound irradiation, the use of ionic liquids or water as new reaction media, solvent-free method have been employed for the synthesis of DHPMs [9]. However, most of the improvement and modification are based on the use of ethyl acetoacetate as one of substrates. According to the existing literature, the reaction conditions and products of ethyl 4,4,4-trifluoroacetoacetate are different from that of the ethyl acetoacetate when it undergoes Biginelli reaction due to the existence of strong electron withdrawing CF_3 group [10]. Considering the difference in the number of fluorine atoms in ethyl 4,4-difluoroacetoacetate, it is desirable to investigate the reactivity of ethyl 4,4-difluoroacetoacetate in the Biginelli reaction. Herein, we reported a simple and efficient synthesis of the difluoromethyl-containing dihydropyrimidinones via Biginelli reaction of ethyl difluoroacetoacetate, urea and aldehydes catalyzed by $Yb(PFO)_3$ under solvent-free conditions without additional dehydrating agent (Table 4).

2. Results and discussion

The only example of using ethyl 4,4-difluoroacetoacetate as an alternative substrate for Biginelli cyclocondensation was reported by Saloutin et al. in 2000 [4]. According to their study, 4-difluoromethyl-4-hydroxy-2-oxo-6-phenyl-hexahydropyrimi-

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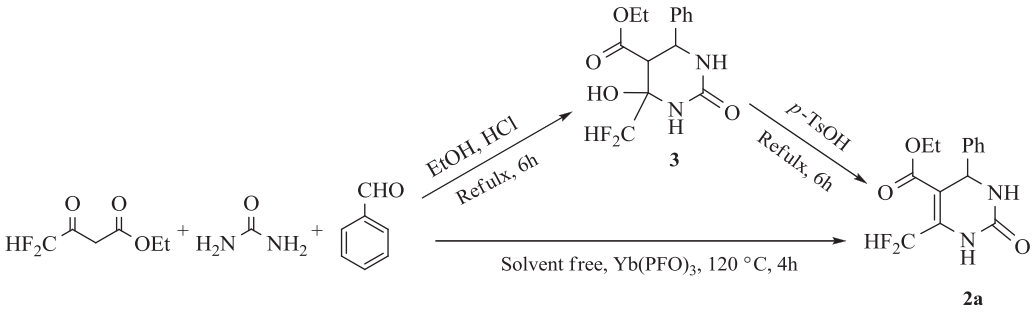


Scheme 1. Two methods for the synthesis of **2a**.

dine-5-carboxylate **3** was obtained via Biginelli reaction coupling of ethyl 4,4-difluoroacetoacetate, benzaldehyde and urea under acidic conditions. Dehydration of **3** in the presence of *p*-toluenesulfonic acid afforded 6-difluoromethyl-5-(ethoxycarbonyl)-4-phenyl-3,4- dihydropyrimidin-2(1*H*)-one **2a** (Scheme 1).

Organic synthesis involving multi-component reactions (MCRs) under solvent-free conditions has been receiving much attention [11]. As a continuation of our research to develop more efficient and practical methods in MCRs [12], we examined the Biginelli solvent-free reactions of ethyl 4,4-difluoroacetoacetate with several aldehydes and urea in the presence of metal catalysts. For our initial studies, ethyl 4,4-difluoroacetoacetate, benzaldehyde and urea were selected as representative substrates to investigate the reaction conditions. To our delight, the reaction proceeded smoothly using 5 mol% metal catalysts under solvent-free conditions at relatively high temperatures to afford the dehydrated compound **2a**, the normal product of the Biginelli reaction (Scheme 1).

The effect of different catalysts on the yields of **2a** under solvent-free conditions at 120 °C was shown in Table 1. When the model reaction was performed in the absence of catalyst, **3** was obtained as the main product, whereas the yield of the dehydrated product **2a** was only 15%. Among the various catalysts tested, $Yb(PFO)_3$ gave high yield of **2a**.

The effect of temperature on the reaction was examined under solvent-free conditions in the presence of $Yb(PFO)_3$. As can be seen from Table 2, the reaction proceeded smoothly at 120 °C giving the expected product in 87% yield. However, the yield of **2a** decreased with decreasing temperature (Table 2).

The effect of amount of catalyst on the reaction was also studied by varying the amount of $Yb(PFO)_3$ under solvent-free conditions (Table 3). It was found that 5 mol% of $Yb(PFO)_3$ was sufficient to carry out this reaction successfully. An increase in the amount of $Yb(PFO)_3$ to more than 5 mol% showed no significant improvement in yield, whereas the yield was reduced by decreasing the amount of $Yb(PFO)_3$ to 2.5 mol%.

In order to determine the limitations of the method, we tested it on several additional aldehydes. Generally, the solvent-free three-component reaction proceeded smoothly to give the expected difluoromethyl-containing dihydropyrimidinones in good to high yields (Table 4). Aromatic aldehydes afforded the higher yields of the desired products than aliphatic aldehydes. In addition, the target compounds (**2a–i**) were easily purified by recrystallization from ethanol without the use of column chromatography.

For comparison, the reaction conditions and products of different types of 1,3-dicarbonyl substrates (ethyl acetoacetate, ethyl 4,4-difluoroacetoacetate and ethyl 4,4,4-trifluoroacetoacetate) for the Biginelli reaction were summarized in Scheme 2. When ethyl acetoacetate used as substrate, the reaction takes place with good yield at 80 °C under solvent-free or reflux conditions and gives the normal 3,4-dihydropyrimidin-2(1*H*)-one products (**I**) [13]. In the case of ethyl 4,4,4-trifluoroacetoacetate, the corresponding trifluoromethyl-containing Biginelli product (**II**) is obtained in the presence of $TaBr_5$ [14], however, an undehydrated product, ethyl 4-(trifluoromethyl) -4-hydroxy-2-oxo-6-phenyl-hexahydropyrimidine-5-carboxylate (**III**) is formed in the presence of other Lewis acid such as $ZrCl_4$ [15]. The intermediate (**III**) can be further dehydrated to (**II**) by using dehydration agents such as *p*-toluenesulfonic acid [8b]. As to our work in this paper, the reaction of ethyl 4,4-difluoroacetoacetate, ethyl acetoacetate, and ethyl 4,4,4-trifluoroacetoacetate with benzaldehyde and urea, respectively, yielded the corresponding normal Biginelli product in good yield in the presence of $Yb(PFO)_3$ under solvent-free conditions, whereas the undesired undehydrated product was not isolated.

In summary, we reported an efficient and practical approach to the synthesis of difluoromethyl-containing dihydropyrimidinones through a solvent-free one-pot three-component condensation of ethyl 4,4-difluoroacetoacetate, aldehydes and urea in the presence of $Yb(PFO)_3$ without additional dehydrating agent.

Table 1
Effect of catalyst on the yields under solvent-free conditions at 120 °C.

Catalyst[a]	Reaction time (h)	**2a** Yield (%)[b]
None	>12	15[c]
HCl	8	34
$ZnCl_2$	4	55
$InCl_3$	4	73
$BiCl_5$	4	72
$(NH_4)_2Ce(NO_3)_6$	4	68
$Yb(PFO)_3$	4	87

[a] Amount of catalysts 5 mol%.
[b] Yields were based on GC analysis.
[c] Compound **3** was a major product.

Table 2
Effect of temperature on the one-pot reaction under solvent-free conditions[a].

Temperature (°C)	Reaction time (h)	**2a** Yield (%)[b]
60	>12	30
80	4	55
100	4	81
120	4	87

[a] Catalyst: 5 mol% of $Yb(PFO)_3$.
[b] Yields were based on GC analysis.

3. Experimental

3.1. Materials and instruments

All reagents were of analytic grade and obtained from commercial suppliers and used without further purification. Melting points were measured in an open capillary using Büchi melting point B-540 apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Bruker AM-400 spectrometer

Table 3
Optimization of amount of catalyst.

Amount of $Yb(PFO)_3$ (mol%)	Reaction time (h)	**2a** Yield (%)[a]
2.5	6	77
5	4	88
7.5	4	91
10	4	93

[a] Yields were based on GC analysis.

(400 MHz and 100 MHz, respectively) using TMS as the internal standard. The ^{19}F NMR spectra were recorded Bruker AM-400 spectrometer (376 MHz) using CF_3CO_2H as external standard. Gas chromatography–mass spectra (GC–MS) were recorded on HP 5973 MSD with 6890 GC. High resolution mass spectra (HRMS) were recorded under electron impact conditions using a Micro-Mass GCT CA 055 instrument and recorded on a MicroMass LCTTM spectrometer.

3.2. General procedure for compounds 2a–i

Aldehyde **1** (2 mmol) and urea (3 mmol) were added to a flask and stirred at room temperature for 30 min before the addition of $Yb(PFO)_3$ (0.1 mmol) and ethyl 4,4-difluoroacetoacetate (2 mmol). The mixture was heated to 120 °C and stirred for another 3–4 h. After the reaction was completed (monitored by TLC), the mixture was cooled to room temperature. Then water (20 mL) was added and the solid precipitate was filtered, washed with cold water. The crude product was recrystallized from ethanol to give the pure product **2**.

3.2.1. 6-Difluoromethyl-5-(ethoxycarbonyl)-4-phenyl-3,4-dihydropyrimidin-2(1H)-one (2a)

White solid, mp 190.2–190.7 °C. ^1H NMR ($CDCl_3$): δ = 1.18 (t, J = 7.0 Hz, 3H), 4.13 (q, J = 6.5 Hz, 2H), 5.43 (s, 1H), 6.11 (s, 1H), 7.32 (s, 5H), 7.39 (t, J_{HF} = 54.0 Hz, 1H), 7.71 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$): δ = 13.9, 55.7, 61.3, 106.0 (t, $^3J_{CF}$ = 6.1 Hz), 108.2 (t, $^1J_{CF}$ = 241.2 Hz), 126.6, 128.5, 128.9, 139.1 (t, $^2J_{CF}$ = 23.8 Hz), 142.0, 152.0, 163.6 ppm. ^{19}F NMR ($CDCl_3$): δ = −122.85 (d, J = 54.0 Hz, 1F), −123.07 (d, J = 54.0 Hz, 1F) ppm. HRMS (EI) for $C_{14}H_{14}F_2N_2O_3$, Calcd: 296.0972, Found: 296.0971.

3.2.2. 6-Difluoromethyl-5-(ethoxycarbonyl)-4-(4-methylphenyl)-3,4-dihydropyrimidin-2(1H)-one (2b)

White solid, mp 193.5–194.4 °C. ^1H NMR ($CDCl_3$): δ = 1.19 (t, J = 7.1 Hz, 3H), 2.33 (s, 3H), 4.13 (q, J = 7.1 Hz, 2H), 5.40 (s, 1H), 6.07 (s, 1H), 7.12–7.21 (m, 4H), 7.39 (t, J_{HF} = 53.7 Hz, 1H), 7.70 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$): δ = 13.9, 21.1, 55.5, 61.3, 106.2 (t, $^3J_{CF}$ = 6.0 Hz), 108.2 (t, $^1J_{CF}$ = 241.4 Hz), 126.5, 129.6, 138.5, 138.8 (t, $^2J_{CF}$ = 23.0 Hz), 139.1, 151.6, 163.6 ppm. ^{19}F NMR ($CDCl_3$): δ = −122.80 (d, J = 53.7 Hz, 1F), −123.08 (d, J = 53.7 Hz, 1F) ppm. HRMS (EI) for $C_{15}H_{16}F_2N_2O_3$, Calcd: 310.1129, Found: 310.1128.

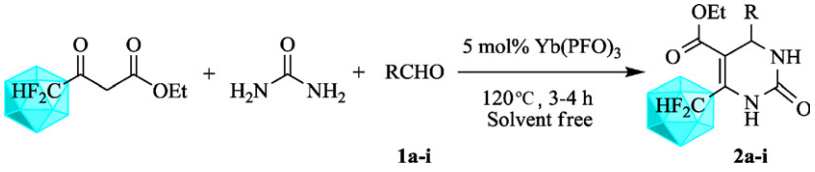
3.2.3. 6-Difluoromethyl-5-(ethoxycarbonyl)-4-(2-methylphenyl)-3,4-dihydropyrimidin-2(1H)-one (2c)

White solid, mp 229.9–231.4 °C. ^1H NMR (DMSO-d_6): δ = 0.99 (t, J = 7.0 Hz, 3H), 2.41 (s, 3H), 3.93–3.96 (m, 2H), 5.48 (s, 1H), 7.16–7.17 (m, 4H), 7.44 (t, J_{HF} = 53.3 Hz, 1H), 7.82 (s, 1H), 9.68 (s, 1H) ppm. ^{13}C NMR (DMSO-d_6): δ = 14.0, 19.1, 51.0, 61.0, 105.3 (t, $^3J_{CF}$ = 6.1 Hz), 109.0 (t, $^1J_{CF}$ = 239.2 Hz), 126.8, 127.2, 128.2, 130.9, 135.4, 140.9 (t, $^2J_{CF}$ = 23.0 Hz), 142.0, 151.5, 164.1 ppm. ^{19}F NMR (DMSO-d_6): δ = −121.3 (d, J = 53.3 Hz, 1F), −121.6 (d, J = 53.3 Hz, 1F) ppm. HRMS (EI) for $C_{15}H_{16}F_2N_2O_3$, Calcd: 310.1129, Found: 310.1130.

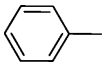
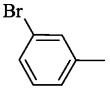
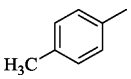
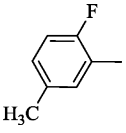
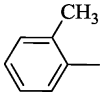
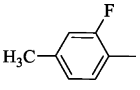
3.2.4. 4-(3-Bromophenyl)-6-difluoromethyl-5-(ethoxycarbonyl)-3,4-dihydropyrimidin-2(1H)-one (2d)

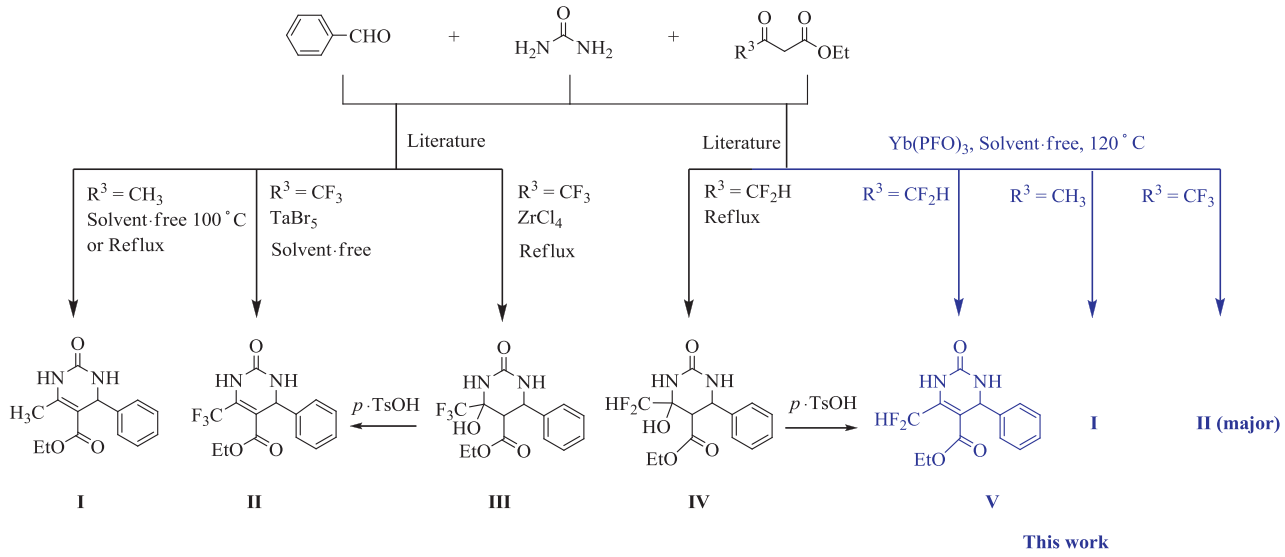
White solid, mp 235.9–237.2 °C. ^1H NMR (DMSO-d_6): δ = 1.12 (t, J = 7.1 Hz, 3H), 4.01–4.13 (m, 2H), 5.24 (s, 1H), 7.25–7.55 (m, 5H), 7.99 (s, 1H), 9.83 (s, 1H) ppm. ^{13}C NMR (DMSO-d_6): δ = 14.2, 53.9, 61.2, 104.6 (t, $^3J_{CF}$ = 6.1 Hz), 109.0 (t, $^1J_{CF}$ = 239.6 Hz), 122.2, 125.7, 129.7, 131.2, 131.5, 141.2 (t, $^2J_{CF}$ = 23.2 Hz), 146.2, 151.9, 164.0 ppm. ^{19}F NMR (DMSO-d_6): δ = −121.3 (s, 1F), −121.4 (s, 1F) ppm. HRMS (EI) for $C_{14}H_{13}BrF_2N_2O_3$, Calcd: 374.0078, Found: 374.0079.

Table 4
Yields of difluoromethyl dihydropyrimidinones **2a–i**.



1a-i 2a-i

Compd.	R	Isolated yield (%)	Compd.	R	Isolated yield (%)	Compd.	R	Isolated yield (%)
2a		86	**2d**		81	**2g**	$(CH_3)_2CHCH_2$–	77
2b		82	**2e**		88	**2h**	$CH_3CH_2CH_2$–	81
2c		83	**2f**		82	**2i**	$(CH_3)_2CH$–	78



Scheme 2. The comparison of reaction conditions and products among the different 1,3-carbonyl substrates for the Biginelli reaction.

*3.2.5. 6-Difluoromethyl-5-(ethoxycarbonyl)-4-(2-fluoro-5-methylphenyl)-3,4-dihydropyrimidin-2(1H)-one (**2e**)*

White solid, mp 224.2–225.0 °C. ^{1}H NMR ($CDCl_3$): δ = 1.14 (t, J = 7.1 Hz, 3H), 2.29 (s, 3H), 4.11 (q, J = 7.1 Hz, 2H), 5.74 (s, 1H), 5.95 (s, 1H), 6.91–7.07 (m, 3H), 7.48 (t, J_{HF} = 53.9 Hz, 1H), 7.83 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$): δ = 13.7, 20.7, 49.7, 61.3, 103.8 (t, $^3J_{CF}$ = 5.7 Hz), 108.0 (t, $^1J_{CF}$ = 241.4 Hz), 115.6 (d, J_{CF} = 21.8 Hz), 127.9 (d, J_{CF} = 13.2 Hz), 128.5 (d, J_{CF} = 3.4 Hz), 130.8 (d, J_{CF} = 8.1 Hz), 134.3 (d, J_{CF} = 3.30 Hz), 140.4 (t, $^2J_{CF}$ = 23.11 Hz), 151.5, 158.2 (d, J_{CF} = 245.1 Hz), 163.4 ppm. ^{19}F NMR ($CDCl_3$): δ = −123.07 (d, J = 53.9 Hz, 1F), −123.21 (d, J = 53.9 Hz, 1F), −124.86 (s, 1F) ppm. HRMS (EI) for $C_{15}H_{15}F_3N_2O_3$, Calcd: 328.1035, Found: 328.1038.

*3.2.6. 6-Difluoromethyl-5-(ethoxycarbonyl)-4-(2-fluoro-4-methylphenyl)-3,4-dihydropyrimidin-2(1H)-one (**2f**)*

White solid, mp 210.9–211.8 °C. ^{1}H NMR (DMSO-d_6): δ = 1.08 (t, J = 7.0 Hz, 3H), 2.29 (s, 3H), 4.01 (q, J = 7.0 Hz, 2H), 5.48 (s, 1H), 7.00–7.17 (m, 3H), 7.42 (t, J_{HF} = 53.3 Hz, 1H), 7.84 (s, 1H), 9.75 (s, 1H) ppm. ^{13}C NMR (DMSO-d_6): δ = 14.1, 21.0, 49.3, 61.0, 103.6 (t, $^3J_{CF}$ = 6.1 Hz), 108.9 (t, $^1J_{CF}$ = 239.4 Hz), 116.5 (d, J_{CF} = 21.7 Hz), 125.7 (d, J_{CF} = 2.7 Hz), 127.5 (d, J_{CF} = 13.8 Hz), 129.0 (d, J_{CF} = 4.6 Hz), 140.7 (d, J_{CF} = 8.2 Hz), 141.1 (t, $^2J_{CF}$ = 23.0 Hz), 151.6, 159.8 (d, J_{CF} = 246.8 Hz), 164.0 ppm. ^{19}F NMR ($CDCl_3$): δ = −119.54 to −119.49 (m, 1F), −121.47 (d, J = 53.3 Hz, 1F), −121.61 (d, J = 53.3 Hz, 1F) ppm. HRMS (EI) for $C_{15}H_{15}F_3N_2O_3$, Calcd: 328.1035, Found: 328.1033.

*3.2.7. 6-Difluoromethyl-5-(ethoxycarbonyl)-4-isobutyl-3,4-dihydropyrimidin-2(1H)-one (**2g**)*

White solid, mp 168.2–169.7 °C. ^{1}H NMR (DMSO-d_6): δ = 0.88 (d, J = 6.4 Hz, 6H), 1.13–1.25 (m, 4H), 1.41–1.48 (m, 1H), 1.73–1.76 (m, 1H), 4.13–4.18 (m, 3H), 7.36 (t, J_{HF} = 53.4 Hz, 1H), 7.68 (s, 1H), 9.54 (s, 1H) ppm. ^{13}C NMR (DMSO-d_6): δ = 14.3, 21.7, 23.2, 24.0, 45.4, 48.7, 61.0, 106.7 (t, $^3J_{CF}$ = 6.1 Hz), 108.9 (t, $^1J_{CF}$ = 238.7 Hz), 140.6 (t, $^2J_{CF}$ = 22.9 Hz), 152.9, 164.2 ppm. ^{19}F NMR (DMSO-d_6): δ = −121.36 (d, J = 53.4 Hz, 1F), −121.54 (d, J = 53.4 Hz, 1F) ppm. HRMS (EI) for $C_{12}H_{18}F_2N_2O_3$, Calcd: 276.1285, Found: 276.1287.

*3.2.8. 6-Difluoromethyl-5-(ethoxycarbonyl)-4-propyl-3,4-dihydropyrimidin-2(1H)-one (**2h**)*

White solid, mp 174.6–174.8 °C. ^{1}H NMR ($CDCl_3$): δ = 0.94 (t, J = 7.2 Hz, 3H), 1.31 (t, J = 7.1 Hz, 3H), 1.47–1.66 (m, 4H), 4.22–4.29 (m, 2H), 4.36–4.39 (m, 1H), 6.06 (s, 1H), 7.33 (t, J_{HF} = 54.1 Hz, 1H), 7.42 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$): δ = 13.5, 14.0, 17.4, 38.5, 51.4, 61.1, 106.7 (t, $^3J_{CF}$ = 6.0 Hz), 108.1 (t, $^1J_{CF}$ = 239.7 Hz), 139.5 (t, $^2J_{CF}$ = 22.8 Hz), 153.0, 163.7 ppm. ^{19}F NMR ($CDCl_3$): δ = −122.9 (d, J = 54.1 Hz, 1F), −124.1 (d, J = 54.1 Hz, 1F) ppm. HRMS (EI) for $C_{11}H_{16}F_2N_2O_3$, Calcd: 262.1129, Found: 262.1133.

*3.2.9. 6-Difluoromethyl-5-(ethoxycarbonyl)-4-isopropyl-3,4-dihydropyrimidin-2(1H)-one (**2i**)*

White solid, mp 172.4–173.6 °C. ^{1}H NMR ($CDCl_3$): δ = 0.90 (d, J = 6.8 Hz, 3H), 0.95 (d, J = 6.9 Hz, 3H), 1.30 (t, J = 7.1 Hz, 3H), 1.87–1.95 (m, 1H), 4.20–4.26 (m, 2H), 4.28 (s, 1H), 6.24 (s, 1H), 7.35 (t, J_{HF} = 52.3 Hz, 1H), 7.49 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.1, 15.5, 18.4, 34.2, 56.9, 61.2, 105.4 (t, $^3J_{CF}$ = 5.9 Hz), 108.2 (t, $^1J_{CF}$ = 240.7 Hz), 140.1 (t, $^2J_{CF}$ = 22.8 Hz), 153.8, 164.1 ppm. ^{19}F NMR ($CDCl_3$): δ = −122.70 (t, J = 52.3 Hz, 2F) ppm. HRMS (EI) for $C_{11}H_{16}F_2N_2O_3$, Calcd: 262.1129, Found: 262.1137.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jfluchem.2010.12.010.

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