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N-Alkoxymethylation of heterocyclic compounds with diethyl phosphite via cleavage of P–O bond

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ABSTRACT

N-Alkoxymethylation of heterocyclic compounds with diethyl phosphite via cleavage of P–O bond was investigated and a series of *N*3-ethoxymethylated heterocyclic compounds were synthesized. A mechanism in which diethyl phosphite acts as an efficient surrogate of ethanol was proposed and supported by several evidences.

1. Introduction

Dialkyl phosphites, as a kind of useful phosphorus-containing reagents, are widely applied to the synthesis of organophosphonate derivatives, which are an important class of biologically active compounds.[1] A large number of useful transformations have been achieved during the past decades, in which dialkyl phosphites were used as standard nucleophilic species for the construction of C–P bonds, in which various compounds can act as the acceptor, such as imines (ketimines),[2] carbonyl groups,[3] α,β-unsaturated carbonyl compounds,[4] nitroalkenes,[5] and so on. Recently, some new catalyst systems have also been developed to promote the fully using of dialkyl phosphites in different ways (Fig. 1). Among those efficient protocols toward the using of dialkyl phosphite derivatives, cleavage of P–H bond inevitably involved homolytic cleavage[6] as the source of P-centered radicals under radical-initiated conditions or heterolytic cleavage[7] (Fig. 1, path a). Besides, there are few reports showing that dialkyl phosphites could also participate in the construction of C–N and C–O bonds, involving the cleavage of C–O bond (path b).[8] However, to the best of our knowledge, few efforts were devoted to improving P–O bond cleavage and further using dialkyl phosphites as an *O*-nucleophiles to achieve some interesting transformations (path c).

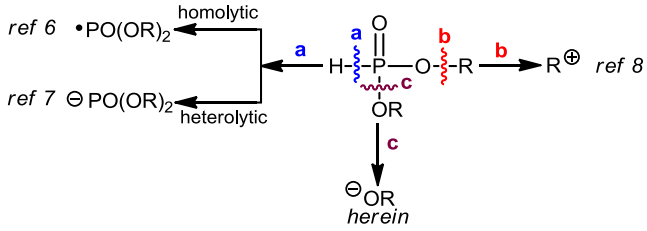

Fig. 1. Reaction of dialkyl phosphites.

In the past decades, 3,4-dihydropyrimidinones (Biginelli compounds or DHPMs) and their derivatives have attracted considerable interest due to their heterocyclic scaffold[9] and interesting pharmacological properties, such as calcium channel modulation, anti-hypertension, α_{1a} adrenergic agonistic and mitotic kinesin inhibition, and hepatitis B virus replication suppression.[10] The *N*-substituted reaction of dihydropyrimidinones is one of the approaches to functionalized dihydropyrimidinones in order to achieve higher bioactive properties.[9] For instance, most of the pharmacologically attractive forms are *N*3-substituted analogues, which might exhibit anti-inflammatory, antihypertensive, analgesic, and anticancer activities.[11] Most *N*-alkylated pyrimidinones are obtained from S_N2 reaction in which pyrimidinone as a nucleophile reacts with an electrophile, such as an alkyl halide and alkyl sulfate. However, unexplained poor regioselectivity between *N*3 and *N*1 were obtained and in most cases *N*1-alkylated products of pyrimidinones were isolated as major products.[9a,b]

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These limitations have hindered the synthesis of *N*3-substituted pyrimidinone derivatives.

As part of our ongoing research program on the synthesis of 3,4-dihydropyrimidinone (DHPM) derivatives,[12] we recently reported a regioselective synthesis of the *N*3-functionalized DHPM by reaction of DHPM with paraformaldehyde and various reagents in the presence of chlorotrimethylsilane.[13] In continuation of our efforts to synthesize some new *N*3-functionalized DHPM derivatives, which might exhibit better biological responses and pharmacological properties, herein we described a novel and efficient synthesis of *N*-ethyoxymethyl-3,4-dihydropyrimidinone using a three component reaction between 3,4-dihydropyrimidinone, paraformaldehyde, and diethyl phosphite via the P–O bond cleavage of diethyl phosphite (Fig. 1, path c).

2. Results and discussion

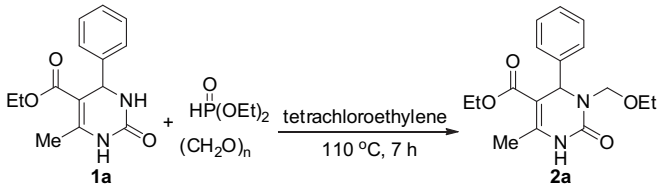
2.1. Reaction with 3,4-dihydropyrimidinone and paraformaldehyde

It has been reported that *N*3-hydroxylmethylated 3,4-dihydropyrimidinone could be achieved by treating 3,4-dihydropyrimidinone with aqueous formaldehyde and potassium carbonate at reflux temperature.[14] According to our mechanism design, we expected that the *N*3-hydroxylmethylated 3,4-dihydropyrimidinones, which produced by the reaction between 3,4-dihydropyrimidinones and paraformaldehyde could subsequently react with diethyl phosphite and generate phosphorus-containing 3,4-dihydropyrimidinone derivatives. However, to our great surprise, P–O bond cleavage occurred and *N*-ethyoxymethyl-3,4-dihydropyrimidinone was isolated as a major product. So we focused our attention on this novel transformation.

Initially, we chose the reaction of DHPM **1a**, paraformaldehyde, and diethyl phosphite as a model reaction to optimize the reaction conditions. The results were summarized in Table 1. An extensive investigation of a range of solvents (all solvents were dried according to standard procedure before use) and catalysts was carried out. The reaction between **1a**, paraformaldehyde, and diethyl phosphite did not occur in refluxing CH_2Cl_2, THF, and ethanol (entries 1–3). A low yield of product **2a** was formed when catalytic amount of $SnCl_2$ or $NiCl_2$ was added (entries 4 and 5). It was found that product **2a** was isolated in 65% yield when the reaction temperature was increased to 80 °C in benzene for 12 h (entry 6). Interestingly, higher yields of **2a** were obtained in tetrachloroethylene (PCE) at 110 °C for 7 h without any catalysis (entries 7 and 8); in contrast, toluene and DMF led to a lower yield of **2a** after 24 h at the same temperature (entries 9 and 10). Lower yields were obtained when the ratio of the substrates was changed (Table 1, entries 11–12). Thus, we decided to use 2 equiv of diethyl phosphite and 2 equiv of paraformaldehyde in PCE at 110 °C without catalysis as the optimal reaction conditions for the preparation of *N*3-ethoxymethyl DHPMs (Table 1, entry 7). We replaced the paraformaldehyde with formaldehyde and the desired product **2** was obtained in low yield (Table 1, entry 13). To confirm the necessity using diethyl phosphite as equivalent of ethanol, we also performed the reaction of **1**, ethanol, and paraformaldehyde under the standard condition, but no any reaction occurred, which implied that it is necessary to use diethyl phosphite as surrogates of the corresponding alcohol.

With these results in hand, we then explored the scope and generality of this three-component reaction (Table 2). Firstly, we varied the substituent on the aromatic ring of **1** to test the electronic effect. From Table 2 we can see, in all cases, the reaction occurred smoothly affording the desired products in good yields. Electron-donating groups (entries 1, 4, and 5) seem propitious to the reaction giving higher yields. This is because the formation of iminium ion **8** would be accelerated when the nucleophilicity of *N*3 was increased (see mechanism). We next investigated the influence of the substituent on R. But no obvious effect was found and even more bulky substituent (*i*-Pr) was tolerated in this reaction (entries 8 and 9). Sulfur-containing analogues of **1** exhibited a slightly lower reactivity, the yields of the desired products decreased about 10%. It is well known that *N*1-methoxymethylation occurred as main reaction by treatment of 3,4-dihydropyrimidinone with chloro(methoxy)methane.[15] However, the NMR spectra of **2a**–**m**, in which **2b** and **2k** were unambiguously confirmed by X-ray crystallography as representative compounds,[16] revealed that the

Table 1
Optimization of reaction conditions for product **2a**[a]



Entry	Equiv of **1a**/$(CH_2O)_n$/DEP	Solvent	Temperature/°C	Time/h	Isolated yield/%
1	1/2/2	CH_2Cl_2	40	24	0
2	1/2/2	THF	65	24	0
3	1/2/2	Ethanol	80	9	0
4[b]	1/2/2	CH_2Cl_2	40	24	35
5[c]	1/2/2	THF	65	12	48
6	1/2/2	Benzene	80	24	65
7	**1/2/2**	**PCE**	**110**	**7**	**84**
8[c]	1/2/2	PCE	110	7	88
9	1/2/2	Toluene	110	24	75
10	1/2/2	DMF	110	24	60
11	1/2/1	PCE	110	7	38
12	1/1/1	PCE	110	7	33
13[d]	1/1/1	PCE	110	7	35

Bold values represent optimal reaction conditions for the preparation of N3-ethoxymethyl DHPMs.

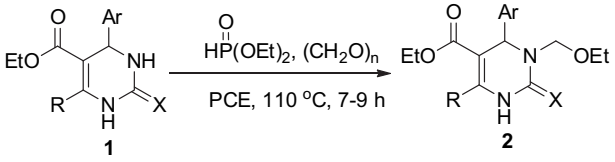
[a] Reaction conditions: DHPM **1a** (1 mmol), $(CH_2O)_n$ (1.5 mmol), and diethyl phosphite (1.5 mmol) in 2 mL solvent.

[b] $SnCl_2$ (0.2 equiv) was used.

[c] $NiCl_2$ (0.2 equiv) was used.

[d] Formaldehyde was used instead of paraformaldehyde.

Table 2
Three-component reaction between dihydropyrimidinones, paraformaldehyde, and diethyl phosphite in PCE[a]



Entry	Ar	R	X	**2**	Time/h	Yield/%
1	C_6H_5	Me	O	**2a**	7	84
2	4-$NO_2C_6H_4$	Me	O	**2b**	8	78
3	3-$NO_2C_6H_4$	Me	O	**2c**	8	81
4	4-MeC_6H_4	Me	O	**2d**	7	88
5	4-$MeOC_6H_4$	Me	O	**2e**	7	90
6	4-FC_6H_4	Me	O	**2f**	7	87
7	4-BrC_6H_4	Me	O	**2g**	7	83
8	C_6H_5	*i*-Pr	O	**2h**	7	84
9	4-$MeOC_6H_4$	*i*-Pr	O	**2i**	7	87
10	C_6H_5	Me	S	**2j**	9	78
11	4-MeC_6H_4	Me	S	**2k**	9	80
12	4-ClC_6H_4	Me	S	**2l**	9	79
13	4-$NO_2C_6H_4$	Me	S	**2m**	9	76

[a] Reaction conditions: DHPMs **1** (1 mmol), $(CH_2O)_n$ (2 mmol), and diethyl phosphite (2 mmol) in 2 mL tetrachloroethylene (PCE) at 110 °C.

reactions of 3,4-dihydropyrimidinones, paraformaldehyde, and diethyl phosphite proceeded in a highly regioselective manner and no any *N*1-substituted product was detected.

2.2. Reaction with NH-heterocyclic compounds 3 and paraformaldehyde

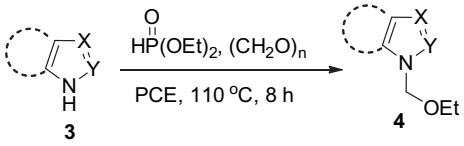
These promising results encouraged us to apply this reaction to other extensive NH-containing heterocycles substrates to further explore the use in construction of more variable heterocyclic compounds via P–O cleavage pattern of diethyl phosphite. To our delight, substrates **3a**–**e** were also able to react with formaldehyde and diethyl phosphite, opening the access to a new type of three-component reaction (Table 3). In this case, benzo[*d*][1,2,3]triazole resulted in *N*1-ethoxymethyl benzo[*d*][1,2,3]triazole (**4aa**) and *N*2-ethoxymethyl benzo[*d*][1,2,3]triazole (**4ab**) with the *N*1-substituted product (**4aa**) as the main product (entry 1). However, reported synthesis of **4a** needed a three-step process, in which benzo[*d*][1,2,3]triazole reacts with formaldehyde to give 1-(hydroxymethyl)benzotriazole, followed by chlorination with thionyl chloride to 1-(chloromethyl) benzotriazole. Subsequently, substitution of the chlorine atom with ethanol gave the products **4a**.[17] Our method based on P–O cleavage of diethyl phosphite has the potential to be a powerful synthetic tool for the construction of such compounds due to its high efficiency.

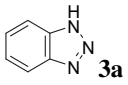
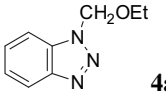
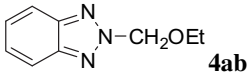
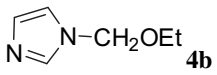
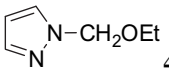
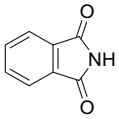
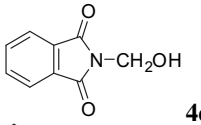
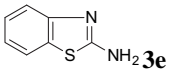
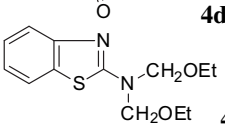
$NiCl_2$ or $SnCl_2$ catalysis; however, only *N*-hydroxymethyl phthalimide (**4d**) was isolated (entry 4). In an attempt to obtain *N*-ethoxymethyl phthalimide, compound **4d** was treated with diethyl phosphite in the presence of $NiCl_2$ or $SnCl_2$ in tetrachloroethylene at 110 °C for 12 h; however, no reaction was observed. This may be due to the strong electron withdrawing conjugation effect of the two carbonyl groups on the nitrogen atom, which reduces the electronic density of the nitrogen atom. Finally, we carried out the reaction of heterocyclic primary amine benzo[*d*] thiazol-2-amine (**3e**), giving the *N*,*N*-bis(ethoxymethyl)benzo[*d*] thiazol-2-amine **4e** in high yield (82%).

2.3. Mechanism

A mechanism was proposed to rationalize the formation of product. First, the NH group of 3,4-dihydropyrimidinone attacked paraformaldehyde, forming an iminium ion **8** (Scheme 1). The hydroxide created in situ initiates a series of electron push processes. The formation of iminium ion **8e** was supported by the LC–MS experimental results (detected at *m*/*z*: 303, 302, 301 for **8e**). Then lone pair electrons in oxygen of diethyl phosphite added to **8** to produce **9**. After that, P–O bond broken producing the corresponding products **2** and monoethyl phosphite.

Table 3
Three-component reaction between NH-heterocycles, paraformaldehyde, and diethyl phosphite in PCE[a]



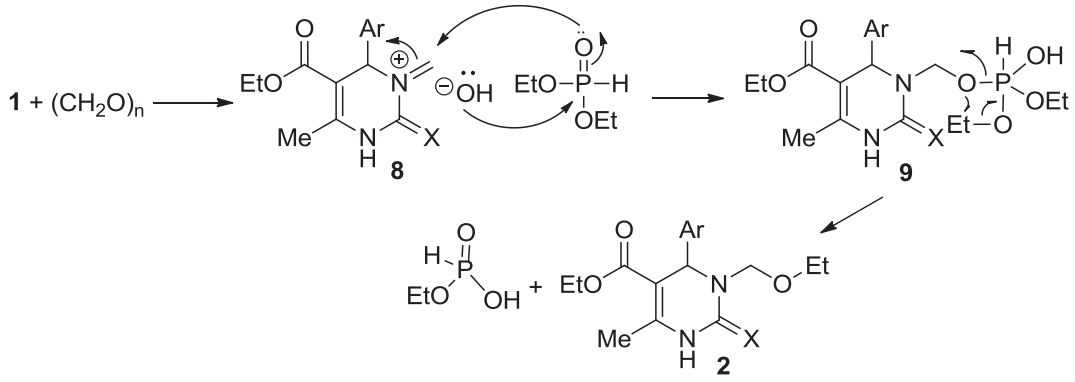
Entry	Material	Product	Isolated yield/%
1	 **3a**	 **4aa**  **4ab**	**4aa**: 78 **4ab**: 16
2	 **3b**	 **4b**	89
3	 **3c**	 **4c**	88[b]
4	 **3d**	 **4d**	84
5	 **3e**	 **4e**	82

[a] Reaction conditions: heterocyclic amines (1 mmol), $(CH_2O)_n$ (2 mmol), and diethyl phosphite (2 mmol) in 2 mL PCE at 110 °C for 8 h.
[b] Detected by NMR and LC–MS.

1*H*-Imidazole (**3b**) and 1*H*-pyrazole (**3c**) were also tolerated in this reaction giving **4b** and **4c** in 89% and 88% yields, respectively (entries 2 and 3). When 1*H*-pyrazole was involved, a mixture of two products was obtained, which could not be isolated by column chromatography and show two sets of closely similar signals in NMR, demonstrating the existence of two compounds (LC–MS also indicates the presence of this product). Phthalimide did not produce any of the desired products in PCE at 110 °C with or without

3. Conclusion

In summary, we have executed a novel approach in which P–O bond cleavage of diethyl phosphite occurred and diethyl phosphite served as an equivalent of alcohol to achieve the synthesis of a series of *N*-ethoxymethylated heterocyclic compounds in high regioselectivity and yield. We are currently focused on promoting this novel transformation and further exploring the use in construction of



Scheme 1. The plausible reaction mechanism.

more variable heterocyclic compounds. Further investigations in the mechanism of this reaction are also underway in this laboratory.

4. Experimental section

4.1. General

All reagents were obtained commercially and used without further purification. Melting points were determined on an XT-4 electrothermal micromelting point apparatus and uncorrected. NMR spectra were recorded at 400 (^{1}H) and 100 (^{13}C) MHz, respectively, on a Varian Mercury plus-400 instrument using $CDCl_3$ as solvent and TMS as internal standard. LC–Mass-spectra and mass-spectra were recorded on a TRACE DSQ instrument. All commercially available substrates were used as received. TLC was performed on 5×10 cm aluminum plates coated with silica gel 60F-254 in an appropriate solvent. All commercially available substrates were used as received.

4.2. General experimental procedure for the reaction of 3,4-dihydropyrimidinones and paraformaldehyde with diethyl phosphite

To a solution of 3,4-dihydropyrimidinone (**1**) (1 mmol) and paraformaldehyde (2 mmol) in tetrachloroethylene (2 mL), diethyl phosphite was added (2 mmol). After completion monitored by TLC, the reaction mixture was concentrated under reduced pressure. The products were separated by silica gel column chromatography eluted with petroleum ethyl acetate/petroleum ether.

*4.2.1. Ethyl 1-(ethoxymethyl)-4-methyl-2-oxo-6-phenyl-1,2,3,6-tetrahydropyrimidine-5-carboxylate (**2a**).* White solid, mp 172–174 °C, yield: 84% (ethyl acetate/petroleum ether=1/5); ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.34 (br s, 1H, NH), 7.39–7.24 (m, 5H, H_{Ar}), 5.50 (s, 1H, 4-CH), 5.21 (d, J=10.8 Hz, 1H, NC*H*H), 4.37 (d, J=10.8 Hz, 1H, NC*H*H), 4.15–4.03 (m, 2H, OCH_2CH$_3$), 3.60–3.54 (m, 1H, OCH_2CH$_3$), 3.46–3.38 (m, 1H, OCH_2CH$_3$), 2.35 (s, 3H, 6-CH$_3$), 1.26–1.22 (m, 3H, OCH$_2$CH_3), 1.18–1.12 (m, 3H, OCH$_2$CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=165.5, 153.3, 145.9, 141.8, 128.4, 127.9, 127.4, 102.3, 74.1, 63.7, 60.0, 57.9, 18.4, 14.9, 14.2. MS: m/z=318 (M^+). Anal. Calcd for $C_{17}H_{22}N_2O_4$ (318.16): C 64.13, H 6.97, N 8.80. Found: C 63.95, H 6.88, N 8.91.

*4.2.2. Ethyl 1-(ethoxymethyl)-4-methyl-6-(4-nitrophenyl)-2-oxo-1,2,3,6-tetrahydropyrimidine-5-carboxylate (**2b**).* White solid, mp 160–161 °C, yield: 78% (ethyl acetate/petroleum ether=1/10); ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.69 (br s, 1H, NH), 8.18 (d, J=8.8 Hz, 2H, H_{Ar}), 7.57 (d, J=8.4 Hz, 2H, H_{Ar}), 5.61 (s, 1H, 4-CH), 5.15 (d, J=10.8 Hz, 1H, NC*H*H), 4.46 (d, J=10.8 Hz, 1H, NC*H*H), 4.15–4.09 (m, 2H, OCH_2CH$_3$), 3.55 (q, J=6.8 Hz, 1H, OCH_2CH$_3$), 3.38 (q, J=6.8 Hz, 1H, OCH_2CH$_3$), 2.37 (s, 3H, 6-CH$_3$), 1.24 (t, J=6.8 Hz, 3H, OCH$_2$CH_3), 1.09 (t, J=6.8 Hz, 3H, OCH$_2$CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=165.0, 153.0, 149.1, 147.5, 146.9, 128.2, 123.8, 101.3, 74.6, 63.9, 60.3, 57.7, 18.5, 14.7, 14.1. MS: m/z=363 (M^+). Anal. Calcd for $C_{17}H_{21}N_3O_6$ (363.14): calcd C 56.19, H 5.83, N 11.56. Found: C 56.31, H 5.79, N 11.64.

*4.2.3. Ethyl 1-(ethoxymethyl)-4-methyl-6-(3-nitrophenyl)-2-oxo-1,2,3,6-tetrahydropyrimidine-5-carboxylate (**2c**).* White solid, mp 168–170 °C, yield: 81% (ethyl acetate/petroleum ether=1/5); ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.62 (br s, 1H, NH), 8.25–7.49 (m, 4H, H_{Ar}), 5.62 (s, 1H, 4-CH), 5.16 (d, J=10.8 Hz, 1H, NC*H*H), 4.48 (d, J=10.8 Hz, 1H, NC*H*H), 4.16–4.06 (m, 2H, OCH_2CH$_3$), 3.59–3.52 (m, 1H, OCH_2CH$_3$), 3.43–3.36 (m, 1H, OCH_2CH$_3$), 2.38 (s, 3H, 6-CH$_3$), 1.26–1.21 (m, 3H, OCH$_2$CH_3), 1.11–1.07 (m, 3H, OCH$_2$CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=165.0, 153.1, 148.2, 147.1, 144.2, 133.4, 129.5, 122.9, 122.4, 101.3, 74.6, 63.9, 60.3, 57.7, 18.4, 14.7, 14.1. MS: m/z=363 (M^+). Anal. Calcd for $C_{17}H_{21}N_3O_6$ (363.14): calcd C 56.19, H 5.83, N 11.56. Found: C 56.30, H 5.79, N 11.62.

*4.2.4. Ethyl 1-(ethoxymethyl)-4-methyl-2-oxo-6-p-tolyl-1,2,3,6-tetrahydropyrimidine-5-carboxylate (**2d**).* White solid, mp 173–175 °C, yield: 88% (ethyl acetate/petroleum ether=1/6); ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.39 (br s, 1H, NH), 7.27–7.22 (m, 2H, H_{Ar}), 7.11–7.06 (m, 2H, H_{Ar}), 5.47 (s, 1H, 4-CH), 5.23 (d, J=10.4 Hz, 1H, NC*H*H), 4.34 (d, J=10.4 Hz, 1H, NC*H*H), 4.15–4.06 (m, 2H, OCH_2CH$_3$), 3.62–3.57 (m, 1H, OCH_2CH$_3$), 3.47–3.39 (m, 1H, OCH_2CH$_3$), 2.30 (s, 3H, 6-CH$_3$), 1.26–1.19 (m, 3H, OCH$_2$CH_3), 1.17–1.11 (m, 3H, OCH$_2$CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=165.5, 153.3, 145.9, 138.9, 137.7, 129.1, 127.3, 102.4, 73.9, 63.8, 60.0, 57.6, 21.1, 18.4, 14.8, 14.2. MS : m/z=332 (M^+), $C_{18}H_{24}N_2O_4$ (332.17): calcd C 65.04, H 7.28, N 8.43. Found: C 65.19, H 7.40, N 8.32.

*4.2.5. Ethyl 1-(ethoxymethyl)-6-(4-methoxyphenyl)-4-methyl-2-oxo-1,2,3,6-tetrahydropyrimidine-5-carboxylate (**2e**).* White solid, mp 134–136 °C, yield: 90% (ethyl acetate/petroleum ether=1/6); ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.51 (br s, 1H, NH), 7.30–7.27 (m, 2H, H_{Ar}), 6.83–6.81 (m, 2H, H_{Ar}), 5.45 (s, 1H, 4-CH), 5.34 (d, J=10.4 Hz, 1H, NC*H*H), 4.35 (d, J=10.4 Hz, 1H, NC*H*H), 4.11–4.05 (m, 2H, OCH_2CH$_3$), 3.80 (s, 3H, OCH$_3$), 3.61–3.57 (m, 1H, OCH_2CH$_3$), 3.52–3.42 (m, 1H, OCH_2CH$_3$), 2.37 (s, 3H, 6-CH$_3$), 1.24–1.16 (m, 6H, OCH$_2$CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=165.5, 153.3, 145.9, 138.9, 137.7, 129.1, 127.3, 102.4, 73.9, 63.8, 60.0, 57.6, 21.1, 18.4, 14.9, 14.2. MS: m/z=348 (M^+). Anal. Calcd for $C_{18}H_{24}N_2O_5$ (348.17): C 62.05, H 6.94, N 8.04. Found: C 62.21, H 6.88, N 8.25.

*4.2.6. Ethyl 1-(ethoxymethyl)-6-(4-fluorophenyl)-4-methyl-2-oxo-1,2,3,6-tetrahydropyrimidine-5-carboxylate (**2f**).* White solid, mp 164–166 °C, yield: 87% (ethyl acetate/petroleum ether=1/5); ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.48 (br s, 1H, NH), 7.36–6.96 (m, 4H,

H_{Ar}), 5.48 (s, 1H, 4-CH), 5.18 (d, J=10.8 Hz, 1H, NC*H*H), 4.38 (d, J=10.8 Hz, 1H, NC*H*H), 4.13–4.06 (m, 2H, OCH_2CH$_3$), 3.58–3.54 (m, 1H, OCH_2CH$_3$), 3.42–3.38 (m, 1H, OCH_2CH$_3$), 2.35 (s, 3H, 6-CH$_3$), 1.26–1.21 (m, 3H, OCH$_2$CH_3), 1.19–1.11 (m, 3H, OCH$_2$CH_3); ^{13}C NMR (100 MHz, CDCl$_3$): δ=165.3, 163.5, 153.4, 146.0, 137.7, 129.1, 115.4, 102.2, 74.1, 63.8, 60.1, 57.3, 18.3, 14.8, 14.1. MS: m/z=352 (M^+). Anal. Calcd for $C_{17}H_{21}FN_2O_4$ (336.15): calcd C 60.70, H 6.29, N 5.65. Found: C 60.79, H 6.34, N 5.58.

*4.2.7. Ethyl 6-(4-bromophenyl)-1-(ethoxymethyl)-4-methyl-2-oxo-1,2,3,6-tetrahydropyrimidine-5-carboxylate (**2g**).* White solid, mp 170–172 °C, yield: 83% (ethyl acetate/petroleum ether=1/5); ^{1}H NMR (400 MHz, CDCl$_3$): δ=8.17 (br s, 1H, NH), 7.43–7.24 (m, 4H, H_{Ar}), 5.46 (s, 1H, 4-CH), 5.18 (d, J=10.4 Hz, 1H, NC*H*H), 4.37 (d, J=10.4 Hz, 1H, NC*H*H), 4.12–4.07 (m, 2H, OCH_2CH$_3$), 3.56 (q, J=6.8 Hz, 1H, OCH_2CH$_3$), 3.40 (q, J=6.8 Hz, 1H, OCH_2CH$_3$), 2.35 (s, 3H, 6-CH$_3$), 1.22 (t, J=6.8 Hz, 3H, OCH$_2$CH_3), 1.13 (t, J=6.8 Hz, 3H, OCH$_2$CH_3); ^{13}C NMR (100 MHz, CDCl$_3$): δ=165.3, 153.2, 146.3, 140.9, 131.6, 129.1, 121.8, 101.8, 74.2, 63.8, 60.1, 57.5, 18.4, 14.8, 14.1. MS: m/z=396 (M^+). Anal. Calcd for $C_{17}H_{21}BrN_2O_4$ (396.07): calcd C 51.40, H 5.33, N 7.05. Found: C 51.34, H 5.37, N 7.09.

*4.2.8. Methyl 1-(ethoxymethyl)-4-isopropyl-2-oxo-6-phenyl-1,2,3,6-tetrahydropyrimidine-5-carboxylate (**2h**).* White solid, mp 154–156 °C, yield: 84% (ethyl acetate/petroleum ether=1/10); ^{1}H NMR (400 MHz, CDCl$_3$): δ=7.35 (br s, 1H, NH), 7.34–7.24 (m, 5H, H_{Ar}), 5.48 (s, 1H, 4-CH), 5.18 (d, J=10.8 Hz, 1H, NCH*H*), 4.41 (d, J=10.8 Hz, 1H, NC*H*H), 4.20–4.13 (m, 1H, 6-CH), 3.67–3.53 (s, 3H, OCH_3), 3.43–3.28 (m, 2H, OCH_2CH$_3$), 2.36 (s, 3H, 6-CH$_3$), 1.21–1.17 (m, 6H, CH(CH_3)$_2$), 1.13–1.09 (m, 3H, OCH$_2$CH_3); ^{13}C NMR (100 MHz, CDCl$_3$): δ=165.7, 154.3, 141.9, 128.5, 127.9, 127.2, 100.7, 74.3, 63.7, 58.0, 51.1, 27.3, 19.6, 19.5, 14.8. MS: m/z=332 (M^+). Anal. Calcd for $C_{18}H_{24}N_2O_4$ (332.17): calcd C 65.04, H 7.28, N 8.43. Found: C 64.95, H 7.84, N 8.47.

*4.2.9. Methyl 1-(ethoxymethyl)-4-isopropyl-6-(4-methoxyphenyl)-2-oxo-1,2,3,6-tetrahydropyrimidine-5-carboxylate (**2i**).* White solid, mp 134–136 °C, yield: 87% (ethyl acetate/petroleum ether=1/10); ^{1}H NMR (400 MHz, CDCl$_3$): δ=7.41 (br s, 1H, NH), 7.27–6.80 (m, 4H, H_{Ar}), 543 (s, 1H, 4-CH), 4.39 (d, J=10.8 Hz, 1H, NC*H*H), 4.18 (d, J=10.8 Hz, 1H, NC*H*H), 4.15–4.11 (m, 1H, 6-CH), 3.81–3.73 (s, 3H, OCH_3), 3.64–3.52 (s, 3H, OCH_3), 3.44–3.28 (m, 2H, OCH_2CH$_3$), 1.34–1.17 (m, 6H, CH (CH_3)$_2$), 1.16–1.12 (m, 3H, OCH$_2$CH_3); ^{13}C NMR (100 MHz, CDCl$_3$): δ=165.7, 159.2, 153.9, 134.0, 128.4, 113.8, 100.9, 74.1, 63.7, 57.3, 55.1, 51.1, 27.3, 19.6, 14.9. MS: m/z=362 (M^+). Anal. Calcd for $C_{19}H_{26}N_2O_5$ (362.18): calcd C 62.97, H 7.23, N 7.73. Found: C 63.05, H 7.20, N 7.84.

*4.2.10. Ethyl 1-(ethoxymethyl)-4-methyl-6-phenyl-2-thioxo-1,2,3,6-tetrahydropyrimidine-5-carboxylate (**2j**).* White solid, mp 118–119 °C, yield: 78% (ethyl acetate/petroleum ether=1/10); ^{1}H NMR (400 MHz, CDCl$_3$): δ=8.06 (br s, 1H, NH), 7.34–7.26 (m, 5H, H_{Ar}), 5.93 (d, J=10.8 Hz, 1H, NC*H*H), 5.68 (s, 1H, 4-CH), 4.66 (d, J=10.8 Hz, 1H, NC*H*H), 4.18–4.11 (m, 2H, OCH_2CH$_3$), 3.68–3.64 (m, 1H, OCH_2CH$_3$), 3.55–3.51 (m, 1H, OCH_2CH$_3$), 2.36 (s, 3H, 6-CH$_3$), 1.25 (t, J=7.2 Hz, 3H, OCH$_2$CH_3), 1.16 (t, J=7.2 Hz, 3H, OCH$_2$CH_3); ^{13}C NMR (100 MHz, CDCl$_3$): δ=176.5, 165.1, 142.2, 140.5, 128.7, 128.3, 127.1, 103.7, 79.2, 64.6, 60.4, 57.2, 18.1, 14.9, 14.1. MS: m/z=334 (M^+). Anal. Calcd for $C_{17}H_{22}N_2O_3S$ (334.14): calcd C 61.05, H 6.63, N 8.38. Found: C 61.12, H 6.67, N 8.35.

*4.2.11. Ethyl 1-(ethoxymethyl)-4-methyl-2-thioxo-6-p-tolyl-1,2,3,6-tetrahydropyrimidine-5-carboxylate (**2k**).* White solid, mp 122–124 °C, yield: 80% (ethyl acetate/petroleum ether=1/10); ^{1}H NMR (400 MHz, CDCl$_3$): δ=8.07 (br s, 1H, NH), 7.29–7.13 (m, 4H, H_{Ar}), 5.97 (d, J=10.8 Hz, 1H, NC*H*H), 5.67 (s, 1H, 4-CH), 4.65 (d, J=10.8 Hz, 1H, NC*H*H), 4.20–4.15 (m, 2H, OCH_2CH$_3$), 3.71–3.65 (m, 1H, OCH_2CH$_3$), 3.59–3.55 (m, 1H, OCH_2CH$_3$), 2.38 (s, 3H, CH$_3$), 2.36 (s, 3H, 6-CH$_3$), 1.28 (t, J=7.2 Hz, 3H, OCH$_2$CH_3), 1.21 (t, J=7.2 Hz, 3H, OCH$_2$CH_3); ^{13}C NMR (100 MHz, CDCl$_3$): δ=176.4, 165.2, 142.0, 138.1, 137.5, 129.3, 127.0, 103.8, 79.0, 64.6, 60.3, 56.9, 21.0, 18.0, 14.9, 14.1. MS: m/z=348 (M^+). Anal. Calcd for $C_{18}H_{24}N_2O_3S$ (348.15): calcd C 62.04, H 6.94, N 8.04. Found: C 62.13, H 6.98, N 8.00.

*4.2.12. Ethyl 6-(4-chlorophenyl)-1-(ethoxymethyl)-4-methyl-2-thioxo-1,2,3,6-tetrahydropyrimidine-5-carboxylate (**2l**).* White solid, mp 128–130 °C, yield: 79% (ethyl acetate/petroleum ether=1/10); ^{1}H NMR (400 MHz, CDCl$_3$): δ=8.19–8.18 (m, 2H, H_{Ar}), 8.17 (br s, 1H, NH), 7.54–7.51 (m, 2H, H_{Ar}), 5.83 (d, J=10.4 Hz, 1H, NC*H*H), 5.79 (s, 1H, 4-CH), 4.76 (d, J=10.4 Hz, 1H, NC*H*H), 4.22–4.16 (m, 2H, OCH_2CH$_3$), 3.66–3.62 (m, 1H, OCH_2CH$_3$), 3.52–3.48 (m, 1H, OCH_2CH$_3$), 2.38 (s, 3H, CH$_3$), 1.28 (t, J=7.2 Hz, 3H, OCH$_2$CH_3), 1.13 (t, J=7.2 Hz, 3H, OCH$_2$CH_3); ^{13}C NMR (100 MHz, CDCl$_3$): δ=176.7, 164.8, 147.6, 143.1, 127.9, 124.0, 102.8, 79.7, 64.8, 60.7, 56.6, 18.3, 14.8, 14.1. MS: m/z=368 (M^+). Anal. Calcd for $C_{17}H_{21}N_2O_3S$ (368.10): calcd C 55.35, H 5.74, N 7.59. Found: C 55.42, H 5.69, N 7.67.

*4.2.13. Ethyl 1-(ethoxymethyl)-4-methyl-6-(4-nitrophenyl)-2-thioxo-1,2,3,6-tetrahydropyrimidine-5-carboxylate (**2m**).* White solid, mp 149–151 °C, yield: 76% (ethyl acetate/petroleum ether=1/10); ^{1}H NMR (400 MHz, CDCl$_3$): δ=8.20 (br s, 1H, NH), 7.30–7.25 (m, 4H, H_{Ar}), 5.90 (d, J=10.8 Hz, 1H, NC*H*H), 5.65 (s, 1H, 4-CH), 4.66 (d, J=10.8 Hz, 1H, NC*H*H), 4.19–4.13 (m, 2H, OCH_2CH$_3$), 3.67–3.61 (m, 1H, OCH_2CH$_3$), 3.56–3.50 (m, 1H, OCH_2CH$_3$), 2.36 (s, 3H, CH$_3$), 1.25 (t, J=7.2 Hz, 3H, OCH$_2$CH_3), 1.16 (t, J=7.2 Hz, 3H, OCH$_2$CH_3); ^{13}C NMR (100 MHz, CDCl$_3$): δ=176.4, 165.0, 142.4, 139.0, 134.1, 128.9, 128.5, 103.3, 79.2, 64.7, 60.5, 56.5, 18.1, 14.9, 14.1. MS: m/z=379 (M^+). Anal. Calcd for $C_{17}H_{21}N_3O_5S$ (379.12): calcd C 53.81, H 5.58, N 11.07. Found: C 53.90, H 5.62, N 10.99.

*4.2.14. 1-(Ethoxymethyl)-1H-benzo[d][1,2,3]triazo (**4aa**).* Colorless liquid, yield: 78% (ethyl acetate/petroleum ether=1/15); ^{1}H NMR (400 MHz, CDCl$_3$): δ=8.05–7.31 (m, 4H, H_{Ar}), 5. 97 (s, 2H, NCH_2), 3.52–3.49 (m, 4H, OCH_2CH$_3$), 1.12–1.11 (m, 3H, OCH$_2$CH_3); ^{13}C NMR (100 MHz, CDCl$_3$): δ=146.2, 132.6, 127.7, 124.1, 119.8, 109.8, 76.8, 64.8, 14.5. MS: m/z=177 (M^+). Anal. Calcd for $C_9H_{11}N_3O$ (177.09): calcd C 61.00, H 6.26, N 23.71. Found: C 61.08, H 6.20, N 23.60.

*4.2.15. 1-(Ethoxymethyl)-1H-benzo[d][1,2,3]triazo (**4ab**).* Colorless liquid, yield: 16% (ethyl acetate/petroleum ether=1/15); ^{1}H NMR (400 MHz, CDCl$_3$): δ=7.92–7.40 (m, 4H, H_{Ar}), 5.94 (s, 2H, NCH_2), 3.69 (q, J=7.2 Hz, 2H, OCH_2CH$_3$), 1.21 (t, J=7.2 Hz, 3H, OCH$_2$CH_3); ^{13}C NMR (100 MHz, CDCl$_3$): δ=144.6, 126.9, 118.4, 84.1, 66.1, 14.6. MS: m/z=175 ($M-2^+$). Anal. Calcd for $C_9H_{11}N_3O$ (177.09): calcd C 61.00, H 6.26, N 23.71. Found: C 61.12, H 6.11, N 23.64.

*4.2.16. 1-(Ethoxymethyl)-1H-imidazole (**4b**).* Yellow oil, yield 89% (ethyl acetate/petroleum ether=1/1); ^{1}H NMR (400 MHz, CDCl$_3$): δ=8.29 (s, 1H, CH), 7.99 (s, 1H, CH), 5.53 (s, 2H, NCH_2), 3.60 (q, J=6.8 Hz, 2H, OCH_2CH$_3$), 1.20 (t, J=6.8 Hz, 3H, OCH$_2$CH_3); ^{13}C NMR (100 MHz, CDCl$_3$): δ=152.0, 143.6, 96.2, 78.0, 65.5, 14.7. MS: m/z=125 ($M-1^+$). Anal. Calcd for $C_6H_{10}N_2O$ (126.08): calcd C 57.12, H 7.99, N 22.21. Found: C 56.98, H 8.04, N 22.30.

*4.2.17. 1-(Ethoxymethyl)-1H-pyrazole (**4c**).* Colorless liquid, yield: 88% (ethyl acetate/petroleum ether=1/1); ^{1}H NMR (400 MHz, CDCl$_3$): δ=8.27 (s, 1H, CH), 7.99 (s. 1H, CH), 5.60 (s, 1H, NCH_2), 5.52 (s, 2H, CH), 3.63–3.55 (m, 2H, OCH_2CH$_3$), 1.20–1.05 (m, 3H, OCH$_2$CH_3); ^{13}C NMR (100 MHz, CDCl$_3$): δ=152.0, 143.6, 95.8, 77.9, 65.4, 14.7. MS: m/z=125 ($M-1^+$). Anal. Calcd for $C_6H_{10}N_2O$ (126.08): calcd C 57.12, H 7.99, N 22.21. Found: C 57.18, H 7.93, N 22.26.

*4.2.18. 2-(Hydroxymethyl)isoindoline-1,3-dione (**4d**).* White solid, mp 168–169 °C, yield: 84% (ethyl acetate/petroleum ether=1/3);

^{1}H NMR (400 MHz, $CDCl_3$): δ=7.93–7.85 (m, 2H, H_{Ar}), 7.79–7.74 (m, 2H, H_{Ar}), 5.26 (d, 2H, NCH_2), 3.14 (br s, 1H, CH_2OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ=134.4, 131.9, 123.7, 61.6. MS: m/z=177 (M^+). Anal. Calcd for $C_9H_7N_2O_3$ (177.04): calcd C 61.02, H 3.98, N 7.91. Found: C 61.11, H 3.93, N 8.00.

*4.2.19. N,N-Bis(ethoxymethyl)benzo[d]thiazol-2-amine (**4e**).* Colorless liquid, yield: 82% (ethyl acetate/petroleum ether=1/15); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.64–7.62 (m, 2H, H_{Ar}), 7.32 (t, J=7.2 Hz, 1H, H_{Ar}), 7.12 (t, J=7.2 Hz, 1H, H_{Ar}), 5.09 (s, 4H, NCH_2), 3.62 (q, J=7.2 Hz, 4H, OCH_2CH$_3$), 1.23 (t, J=7.2 Hz, 6H, OCH$_2$CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=151.9, 143.5, 95.8, 77.9, 65.4, 14.6. MS: m/z=266 (M^+). Anal. Calcd for $C_{13}H_{18}N_2O_2S$ (266.11): calcd C 58.62, H 6.81, N 10.52. Found: C 58.70, H 6.87, N 10.45.

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Supplementary data

These data include the copies of the NMR of the compounds described in this article. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2011.01.061. These data include MOL files and InChiKeys of the most important compounds described in this article.

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