An Efficient One-Pot Synthesis of Pyrimido[2,1-b][1,3]Oxazine Derivatives *via* the Reaction of Isocyanides with Dialkyl Acetylenedicarboxylates in the Presence of 5-Substituted Uracils

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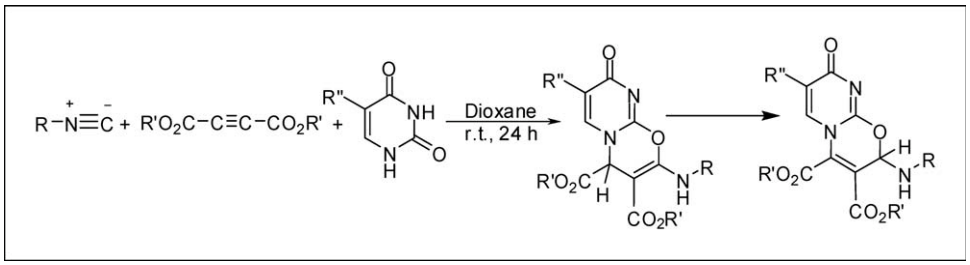

The reactive 1:1 intermediate produced in the reaction between alkyl isocyanides and dialkyl acetylenedicarboxylates was trapped by uracil and its 5-substituted derivatives to yield highly functionalized pyrimido[2,1-b][1,3]oxazine derivatives in fairly good yields.

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INTRODUCTION

In recent years, multicomponent reactions (MCRs) have become important area of research in organic and medicinal chemistry due to their significant advantages over conventional two-component reactions in several aspects, such as flexibility, productivity, convergent, and high-bond forming efficiency. Advances in heterocyclic MCRs methodology have led to success in the drug discovery process. The isocyanide-based MCRs are especially important in this area [1]. Isocyanide nucleophiles have been known to form zwitterions with activated acetylenic compounds such as dialkyl acetylenedicarboxylates [2]. These types of zwitterions can be trapped by a variety of electrophiles such as activated carbonyl compounds [3] or reagents containing NH, OH, or CH acidic groups [4] thus, constituting a novel protocol for the synthesis of heterocyclic and carbocyclic compounds.

Heterocyclic compounds with bridgehead nitrogen form a significant group of natural products and many of them are biologically active compounds, thus, the synthesis of them has attracted much attention of organic chemists [5]. Research on synthesis of 1,3-oxazine derivatives has shown that they have diverse biological properties such as analgesic, anticonvulsant, antibacterial, and antitumor activity [6].

Several methods for the preparations of 1,3-oxazine derivatives have previously been reported [7]. As part of our current studies on the development of new routes in heterocyclic synthesis [8], we wish to report a facile synthesis of functionalized pyrimido[2,1-b][1,3]oxazines *via* trapping of the isocyanide-dialkyl acetylenedicarboxylate intermediates with the acidic NH of 5-substituted uracils.

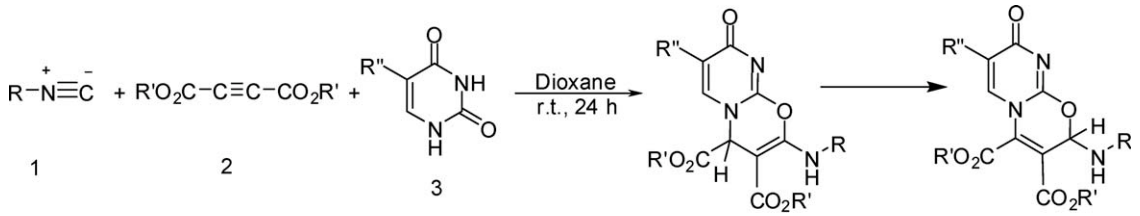
The diverse pharmacological activities of these fused bicycle 6,6-heterocyclic systems encouraged us to develop a concise synthetic route to these compounds.

RESULTS AND DISCUSSION

The reaction of alkyl isocyanides **1** with dialkyl acetylenedicarboxylates **2** in the presence of 5-substituted uracils **3** in 1,4-dioxane at room temperature leads to byproducts **4** which, under the reaction conditions, isomerize to produce 7-alkyl (or halo)-8-oxo-2H,8H-pyrimido[2,1-b][1,3]oxazine-3,4-dicarboxylate derivatives **5** in fairly good yields (Scheme 1).

The reactions were carried out by slow addition of alkyl isocyanides **1** to a mixture of the 5-substituted uracils **3** and dialkyl acetylenedicarboxylates **2** in 1,4-dioxane at room temperature. The reactions proceeded spontaneously and were completed within 24 h. The 5-substituted uracils are weak NH-acids with pK_as in the range of 7.93–9.75, except for the 5-nitro uracil which has a pK_a of 5.66 [9]. The presence of two nonequivalent nitrogen atoms in 5-substituted uracils can, of course, raise the question of regioselectivity and the formation of two regioisomeric products. There are several reports [10] that confirm deprotonation of uracil and its 5-substituted derivatives in basic media which

Scheme 1



1	R
a	tBu
b	Cyclohexyl

2	R'
a	Me
b	Et

3	R''
a	Me
b	H
c	Br
d	F

5	R	R'	R''	%Yield
a	tBu	Me	Me	78
b	tBu	Me	H	75
c	tBu	Me	Br	70
d	tBu	Me	F	85
e	tBu	Et	Me	87
f	tBu	Et	H	78
g	tBu	Et	Br	87
h	tBu	Et	F	80
i	Cyclohexyl	Me	Br	78

subsequently undergo completely regioselective reactions such as N-alkylation and N-arylation, at the N-1 position. Interestingly, the formations of N-3 or O-arylation products were not detected in these reactions. Similarly, when we treated isocyanides **1** with compounds **2** and **3** in dioxane, the ^{1}H- and ^{13}C-NMR spectra of the crude products clearly indicated the regioselective formation of 7-alkyl (or halo)-8-oxo-2H,8H-pyrimido[2,1-b][1,3]oxazine-3,4-dicarboxylates derivatives **5**. The structures of compounds **5a**–**5i** were elucidated from elemental analyses, IR, and high-field ^{1}H- and ^{13}C-NMR spectra. The mass spectrum of **5a** displayed the molecular ion (M^+) signal at 531 *m/z*, that is, consistent with the 1:1:1 adduct of 5-methyl uracil (thymine), dimethyl acetylenedicarboxylate, and *tert*-butyl isocyanide. The ^{1}H-NMR spectrum of **5a** exhibited four sharp singlets arising from *tert*-butyl ($\delta = 1.30$ ppm), two methoxy ($\delta = 3.78$ ppm and 3.92 ppm), and one methine ($\delta = 6.90$ ppm) protons. Also, two singlets were observed at $\delta = 2.03$ ppm and 8.01 ppm for methyl protons and the adjacent vinylic hydrogen, respectively. The NH proton resonance at $\delta = 8.47$ ppm disappeared on the addition of D_2O to the $CDCl_3$ solution of **5a**. The ^{1}H-NMR of byproduct **4a** is similar to that of **5a**, except for the CH group which exhibits a singlet at $\delta = 5.69$ ppm. The proton decoupled ^{13}C-NMR spectrum of **5a** showed 14 distinct signals in agreement with the proposed structure. Partial assignment of these signals is given in ''Experimental'' section.

Unfortunately, our attempts to prepare single crystal of the products for X-ray crystallography were not successful. However, the 2D HMQC, HMBC, and DEPT spectra were used to attribute the structure of **5a** (Fig. 1) and complete ^{1}H and ^{13}C chemical shift assignments are summarized in Table 1. In the HMBC spectrum, the methyl protons of *tert*-butyl at δ 1.30 (s) showed correlation with C-18 (δc 57.38, $^2J_{CH}$). Further the H-21 methyl protons at δ 2.03 (s) showed correlation with the C-8 (δc 165.1, $^3J_{CH}$), C-7 (δc 126.9, $^2J_{CH}$) and C-6 (δc 138.2, $^3J_{CH}$). The H-6a pyrimidine proton at δ 8.01 (s) showed correlations with C-7 (δc 126.9, $^2J_{CH}$), C-4 (δc 140.6, $^3J_{CH}$), C-8 (δc 165.1, $^3J_{CH}$), C-10 (δc 150.3, $^3J_{CH}$), and C-21 (δc 12.9, $^3J_{CH}$). The H-2 oxazine proton at δ 6.90 (s) showed correlations with C-3 (δc 140.6, $^2J_{CH}$) and C-14 (δc 164.1, $^3J_{CH}$). The H-16 and H-13 (methoxy protons) showed correlations with

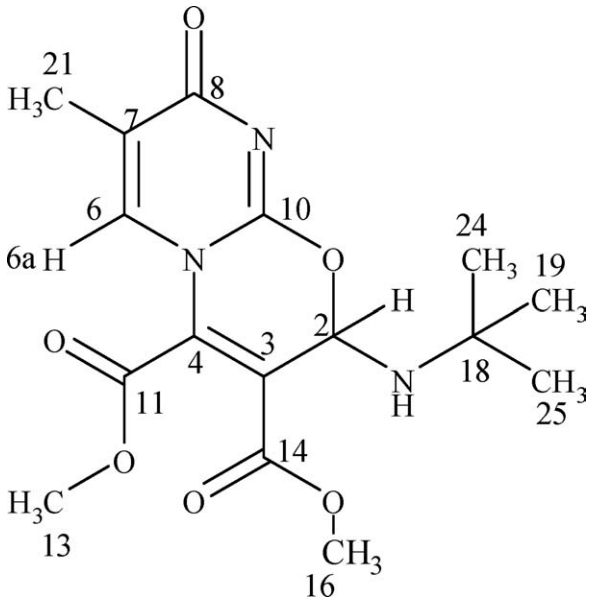


Figure 1. Representation of atom numbers for compound **5a**.

Table 1

^{13}C-NMR (75 MHz), ^{1}H-NMR (500 MHz), HMQC, and HMBC (500 MHz) data for compound **5a**.

	HMQC ($CDCl_3$)		HMBC ($CDCl_3$)	
H	δ_C	δ_H	$^2J_{CH}$	$^2J_{CH}$
19, 24, 25	30.7	1.30	C-18	
21	12.9	2.03	C-7	C-6, C-8
6a	138.2	8.01	C-7	C-4, C-7, C-8, C-10, C-21
2	111.0	6.90	C-3	C-14
13,16	52.8, 53.4	3.78, 3.92		C-11, C-14

C-14 and C-11 (δc 164.1 and 164.4, $^3J_{CH}$). All of the HMBC and HMQC correlations are shown in Figure 2.

The ^{1}H- and ^{13}C-NMR spectra of compounds **5b–5i** are similar to those of **5a**, except for the R″, alkyl amino, and ester groups, which exhibit characteristic signals with appropriate chemical shifts.

A plausible mechanism for this reaction is proposed in Scheme 2. On the basis of the well-established chemistry of isocyanides [11], it is reasonable to assume that the functionalized pyrimido[2,1-b][1,3]oxazines **5** could result from initial addition of the isocyanide to the acetylenic ester and subsequent protonation of 1:1 adduct **6** by compound **3**, followed by attack of the anion **7** of the NH-acid **3** on the positively charged ion **8** to form ketenimine **9**, tautomerizes and cyclizes *via* Intermolecular O-head attack to C_{sp} of ketenimine to form the fused heterocyclic system **4**. Byproducts **4** apparently isomerize, under the reaction conditions, to produce stable conjugated pyrimido oxazines **5**. We could only isolate and identify the heterocyclic system **4a** as a byproduct along with the major product **5a** by silica gel column chromatography. The yields of the other products **4** (**4b–4i**) were too low for isolation and characterization.

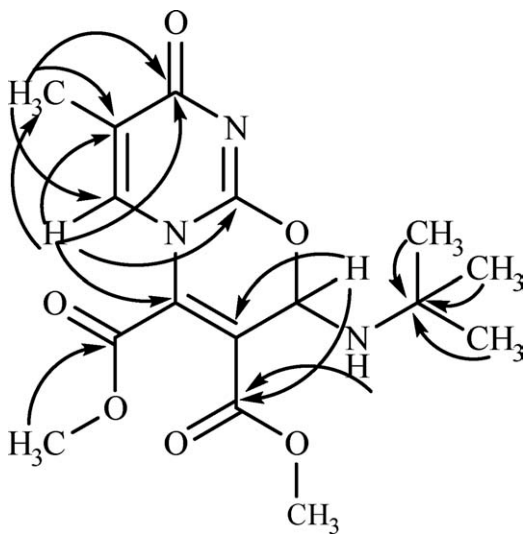


Figure 2. Heteronuclear correlations $^2J_{CH}$ and $^3J_{CH}$ (HMBC) for compound **5a**.

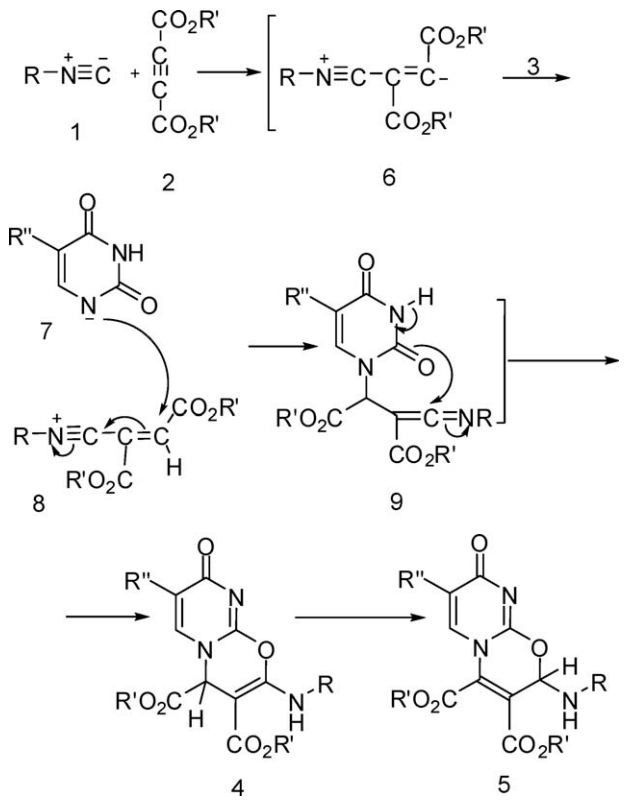
CONCLUSIONS

The present method carries the advantage that not only the reaction is performed under neutral conditions but also the substrates can be mixed without any activation or modification. The simplicity of the present procedure makes this protocol an interesting alternative to other approaches. The procedure described here provides a simple one-pot method for the preparation of polyfunctional pyrimido[2,1-b][1,3]oxazine derivatives with potential synthetic and pharmaceutical interest.

EXPERIMENTAL

Dialkyl acetylenedicarboxylates, 5-substituted uracils, and alkyl isocyanides were obtained from Fluka (Germany) and were used without further purification. Melting points were measured on an Electrothermal 9100 apparatus. Elemental analyses for C, H, and N were performed using a Heraeus CHN-O-Rapid analyzer. Mass spectra were recorded on a FINNIGAN-MATT 8430 mass spectrometer operating at an ionization potential of 20 eV. ^{1}H-, ^{13}C-, and ^{19}F-NMR spectra were recorded on a BRUKER DRX-300 AVANCE

Scheme 2



spectrometer at 300.1, 75.5, and 282.4 MHz, respectively. HMQC and HMBC spectra were measured at 500 MHz for ^{1}H-NMR and at 125 MHz for ^{13}C-NMR. ^{1}H-, ^{13}C-, ^{19}F-NMR, HMQC, HMBC, and DEPT spectra were obtained in $CDCl_3$ using TMS or $CFCl_3$ as internal standard. IR spectra were recorded as KBr pellets on a Shimadzu IR-460 spectrometer. Chromatography columns were prepared from Merck silica gel 60 mesh.

General procedure. To a magnetically stirred solution of 5-substituted uracils (2 mmol) and dialkyl acetylenedicarboxylates (2 mmol) in anhydrous 1,4-dioxane (5 mL), a solution of isocyanide (2 mmol) in 1,4-dioxane (2 mL) over a period of 10 minutes was added dropwise. The reaction mixture was stirred 24 h at room temperature. After completion of the reaction as indicated by TLC, the solvent was removed and the residue was purified by silica gel column chromatography (hexane–ethyl acetate, 3:1) to afford products **4a** and **5a**–**5i**. When necessary, the isolated products were further purified by recrystallization in diethyl ether–dichloromethane.

Dimethyl-2-(tert-butylamino)-7-methyl-8-oxo-4H,8H-pyrimido[2,1-b][1,3]oxazine-3,4-dicarboxylate (4a, $C_{16}H_{21}N_3O_6$). White powder, mp 380–382°C; 0.1 g, yield 14%; IR (υ_{max}/cm^{-1}): NH 3402, C=O 1744 and 1665. ^{1}H-NMR (300.1 MHz, $CDCl_3$): δ 1.49 (9H, s, $C(CH_3)_3$), 1.95 (3H, s, CH_3), 3.76 and 3.81 (6H, 2s, $2OCH_3$), 5.69 (1H, s, NC*H*—CO_2Me), 7.35 (1H, s NCH), 8.95 (1H, br. s, NH). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 12.9 (CH_3), 30.6 [$C(CH_3)_3$], 52.4 and 53.6 ($2OCH_3$), 58.6 [$C(CH_3)_3$], 60.2 (N*C*H—CO_2Me), 63.2 (NH—C=*C*), 110.7 (*C*CH_3), 140.2 (NCH), 151.0 (N=C—O), 161.4 (NH—*C*=C), 164.5, 168.2, and 170.3 (3C=O). MS, *m/z* (%): 351 (M^+, 18), 294 (58), 279 (50), 213 (8), 190 (65), 160 (9), 57 (100), 41 (55). Anal. Calcd for $C_{16}H_{21}N_3O_6$ (351.35): C, 54.69; H, 6.02; N, 11.96. Found: C, 55.35; H, 6.04; N, 11.85%.

Dimethyl-2-(tert-butylamino)-7-methyl-8-oxo-2H,8H-pyrimido[2,1-b][1,3]oxazine-3,4-dicarboxylate (5a, $C_{16}H_{21}N_3O_6$). White powder, mp 380–383°C, 0.61 g, yield 78%. IR (KBr; υ_{max}/cm^{-1}): NH 3332, C=O 1744, 1704, and 1664. ^{1}H-NMR (300.1 MHz, $CDCl_3$): δ 1.30 (9H, s, $C(CH_3)_3$), 2.03 (3H, s, CH_3), 3.78 and 3.92 (6H, 2s, $2OCH_3$), 6.90 (1H, s, NHC*H*O), 8.01 (1H, s, NCH), 8.47 (1H, br. s, NH). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 12.9 (CH_3), 30.7 [$C(CH_3)_3$], 52.8 and 53.4 ($2OCH_3$), 57.4 [$C(CH_3)_3$], 126.9 (*C*CH_3), 111.0 (NHCHO), 138.2 (NCH), 140.6 and 142.4 (2C), 150.3 (N=C—O), 164.0, 164.4, and 165.1 (3C=O). MS, *m/z* (%): 351 (M^+, 10), 294 (65), 279 (54), 213 (4), 190 (55), 160 (7), 138 (30), 72 (8), 57 (100), 41 (45). Anal. Calcd for $C_{16}H_{21}N_3O_6$ (351.35): C, 54.69; H, 6.02; N, 11.96. Found: C, 54.35; H, 6.12; N, 11.95%.

Dimethyl-2-(tert-butylamino)-8-oxo-2H,8H-pyrimido[2,1-b][1,3]oxazine-3,4-dicarboxylate (5b, $C_{15}H_{19}N_3O_6$). White powder, mp 358–362°C, 0.59 g, yield 76%; IR (KBr; υ_{max}/cm^{-1}): NH 3328, C=O 1724, 1694, and 1653. ^{1}H-NMR (300.1 MHz, $CDCl_3$): δ 1.25 [9H, s, $C(CH_3)_3$], 3.74 and 3.89 (6H, 2s, $2OCH_3$), 5.78 and 8.11 (2H, d, $^3J_{HH}$ = 8.3 Hz, 2CH), 6.88 (1H, s, NHC*H*O), 8.96 (1H, br. s, NH). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 30.2 [$C(CH_3)_3$], 52.5 and 53.1 ($2OCH_3$), 57.1 [$C(CH_3)_3$], 126.9 (CH), 102.2 (NHCHO), 139.9 (NCH), 141.8 and 142.5 (2C), 149.9 (N=C—O), 163.5, 163.6, and 164.6 (3C=O). MS, *m/z* (%): 337 (M^+, 5), 281 (58), 266 (52), 190 (53), 138 (33), 119 (10), 57 (100), 41 (43). Anal. Calcd for $C_{15}H_{19}N_3O_6$ (337.33): C, 53.41; H, 5.68; N, 12.46. Found: C, 53.58; H, 5.78; N, 11.95%.

Dimethyl-7-bromo-2-(tert-butylamino)-8-oxo-2H,8H-pyrimido[2,1-b][1,3]oxazine-3,4-dicarboxylate (5c, $C_{15}H_{18}BrN_3O_6$). White powder, mp 373–376°C, 0.66 g, yield 85%; IR (KBr) (υ_{max}/cm^{-1}): NH 3216, C=O 1760, 1744, and 1608. ^{1}H-NMR (300.1 MHz, $CDCl_3$): δ 1.25 [9H, s, $C(CH_3)_3$], 3.76 and 3.89 (6H, 2s, $2OCH_3$), 6.89 (1H, s, NHC*H*O), 8.44 (1H, s, NCH), 8.75 (1H, br. s, NH). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 30.2 [$C(CH_3)_3$], 52.6 and 53.2 ($2OCH_3$), 57.3 [$C(CH_3)_3$], 127.3 (C—Br), 97.9 (NHCHO), 139.2 (NCH), 141.3 and 141.4 (2C), 149.2 (N=C—O), 159.0, 163.4, and 164.5 (3C=O). MS, *m/z* (%): 416 (M^+, 4), 418 [M^++2, 3.8)], 268 (4), 268 (50), 170 (25), 138 (56), 57 (100), 41 (44). Anal. Calcd for $C_{15}H_{18}BrN_3O_6$ (416.22): C, 43.28; H, 4.36; N, 10.10. Found: C, 44.15; H, 4.23; N, 10.05%.

Dimethyl-2-(tert-butylamino)-7-fluoro-8-oxo-2H,8H-pyrimido[2,1-b][1,3]oxazine-3,4-dicarboxylate (5d, $C_{15}H_{18}FN_3O_6$). Yellow oil, 0.62 g, yield 80%; IR (υ_{max}/cm^{-1}): NH 3216, C=O 1760, 1649, and 1608. ^{1}H-NMR (300.1 MHz, $CDCl_3$): δ 1.46 [9H, s, $C(CH_3)_3$], 3.73 and 3.78 (6H, 2s, $2OCH_3$), 6.73 (1H, s, NHC*H*O), 7.67 (1H, d, $^3J_{HF}$ = 5.7 Hz, NCH), 9.55 (1H, br. s, NH). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 30.2 [$C(CH_3)_3$], 52.1 and 53.4 ($2OCH_3$), 57.9 [$C(CH_3)_3$], 96.9 (NHCHO), 128.0 (d, $^2J_{CF}$ = 20.5 Hz, NCH), 140.0 (d, $^1J_{CF}$ = 236.7 Hz, CF), 149.4 (C), 157.2 (d, $^2J_{CF}$ = 26.2 Hz, C=O), 159.9 (C), 163.7 (N—C=O), 167.5 and 169.6 (2C=O). ^{19}F-NMR (282.4 MHz, $CDCl_3$): δ_F −165.48 ($^3J_{HF}$ = 5.7 Hz). MS, *m/z* (%): 416 (M^+), 295 (28), 170 (28), 41 (28), 57 (100). Anal. Calcd for $C_{15}H_{18}FN_3O_6$ (355.32): C, 50.70; H, 5.11; N, 11.83. Found: C, 50.59; H, 5.09; N, 11.09%.

Diethyl-2-(tert-butylamino)-7-methyl-8-oxo-2H,8H-pyrimido[2,1-b][1,3]oxazine-3,4-dicarboxylate (5e, $C_{18}H_{25}N_3O_6$). Yellow oil, 0.62 g, yield 80%; IR (υ_{max}/cm^{-1}): NH 3425, C=O 1755, 1685, and 1675. ^{1}H-NMR (300.1 MHz, $CDCl_3$): δ 1.26 and 1.32 (6H, 2t, $^3J_{HH}$ = 7.1 Hz, $2OCH_2CH_3$), 1.25 [9H, s, $C(CH_3)_3$], 1.97 (3H, s, CH_3), 4.16 and 4.34 (4H, 2qd, $^3J_{HH}$ = 7.1 Hz, $^2J_{HH}$ = 1.1 Hz, $2OCH_2CH_3$), 6.84 (1H, s, NHC*H*O), 7.97 (1H, s, NCH), 9.23 (1H, br. s, NH). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 12.6 and 14.0 ($2OCH_2CH_3$), 30.3 [$C(CH_3)_3$], 56.9 [$C(CH_3)_3$], 61.5 and 62.3 ($2OCH_2CH_3$), 126.9 (*C*CH_3), 110.4 (NHCHO), 137.9 (NCH), 140.4 and 142.0 (2C), 149.9 (N=C—O), 163.1, 164.3, and 164.4 (3C=O). MS, *m/z* (%): 379 (M^+, 12), 338 (44), 332 (38), 293 (7), 233 (35), 231 (50), 146 (15), 57 (100), 41 (58). Anal. Calcd for $C_{18}H_{25}N_3O_6$ (379.41): C, 56.98; H, 6.64; N, 11.08. Found: C, 57.04; H, 6.53; N, 11.12%.

Diethyl-2-(tert-butylamino)-8-oxo-2H,8H-pyrimido[2,1-b][1,3]oxazine-3,4-dicarboxylate (5f, $C_{17}H_{23}N_3O_6$). Yellow oil, 0.60 g, yield 78%; IR (υ_{max}/cm^{-1}): NH 3308, C=O 1704, 1673 and 1642. ^{1}H-NMR (300.1 MHz, $CDCl_3$): δ 1.15 and 1.17 (6H, 2t, $^3J_{HH}$ = 7.1 Hz, $2OCH_2CH_3$), 1.38 [9H, s, $C(CH_3)_3$], 4.10 and 4.15 (4H, 2q, $^3J_{HH}$ = 7.1 Hz, $2OCH_2CH_3$), 5.62 and 7.49 (2H, 2d, $^3J_{HH}$ = 8.1 Hz, 2CH), 7.23 (1H, s, NHC*H*O), 10.04 (1H, br. s, NH). ^{13}C-NMR (75.5 MHz, $CDCl_3$): ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 13.9 and 14.19 ($2OCH_2CH_3$), 30.1 [$C(CH_3)_3$], 62.8 [$C(CH_3)_3$], 65.8 and 70.1 ($2OCH_2CH_3$), 101.6 (CH), 91.1 (NHCHO), 144.1 (NCH), 150.8 and 155.7 (2C), 161.5 (N=C—O), 164.1, 167.1, and 169.3 (3C=O). MS, *m/z* (%): 365 (M^+, 10), 324 (2), 308 (30), 281 (6), 214 (8), 151 (65), 57 (100), 41 (50). Anal. Calcd for $C_{15}H_{19}N_3O_6$ (365.38): C, 55.88; H, 6.34; N, 11.50. Found: C, 55.69; H, 6.25; N, 12.04%.

Diethy-7-bromo-2-(tert-butylamino)-8-oxo-2H,8H-pyrimido [2,1-b][1,3]oxazine-3,4-dicarboxylate (5g, $C_{17}H_{22}BrN_3O_6$). White powder, mp 384–388°C, 0.67 g, yield 87%; IR (KBr) (υ_{max}/cm^{-1}): NH 3452, C=O 1785, 1748, and 1675. ^{1}H-NMR (300.1 MHz, $CDCl_3$): δ 1.16–1.27 (6H, m, $2OCH_2CH_3$), 1.43 [9H, s, $C(CH_3)_3$], 4.11–4.29 (4H, m, $2OCH_2CH_3$), 6.47 (1H, s, NHC*H*O), 7.86 (1H, s, N—CH), 9.82 (1H, br. s, NH). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 14.0 and 14.2 ($2OCH_2CH_3$), 30.2 [$C(CH_3)_3$], 53.5 [$C(CH_3)_3$], 58.5 and 60.9 ($2OCH_2CH_3$), 127.9 (C—Br), 96.4 (NHCHO), 138.0 (NCH) 143.4 and 150.1 (2C), 159.6 (N=C—O), 160.5, 166.8, and 169.3 (3C=O). MS, *m/z* (%): 444 (M^+, 12), 446 [M^++2, 11.75)], 403 (4), 387 (28), 363 (15). 230 (65), 214 (10), 81 (25), 57 (100), 41 (45). Anal. Calcd for $C_{17}H_{22}BrN_3O_6$ (444.28): C, 45.96; H, 4.99; N, 9.46. Found: C, 45.85; H, 5.10; N, 9.39%.

Diethyl-2-(tert-butylamino)-7-fluoro-8-oxo-2H,8H-pyrimido [2,1-b][1,3]oxazine-3,4-dicarboxylate (5h, $C_{17}H_{22}FN_3O_6$). Yellow oil, 0.62 g, yield 80%, IR (υ_{max}/cm^{-1}): NH 3435, C=O 1698, 1672 and 1656. ^{1}H-NMR (300.1 MHz, $CDCl_3$): δ 1.16 and 1.22 (6H, 2t, $^3J_{HH}$ = 7.1 Hz, $2OCH_2CH_3$), 1.41 [9H, s, $C(CH_3)_3$], 4.15 and 4.21 (4H, 2q, $^3J_{HH}$ = 7.1 Hz, OCH_2CH_3), 7.28 (1H, s, NHC*H*O), 7.67 (1H, d, $^3J_{HF}$ = 5.7 Hz, NCH), 10.05 (1H, br. s, NH). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 13.9 and 14.2 ($2OCH_2CH_3$), 30.1 [$C(CH_3)_3$], 59.8 [$C(CH_3)_3$], 60.9 and 62.1 ($2OCH_2CH_3$), 91.0 (NHCHO), 128.1 (d, $^2J_{CF}$ = 20.5 Hz, NCH), 149.0 (d, $^1J_{CF}$ = 236.7 Hz, CF), 149.5 (C), 157.3 (d, $^2J_{CF}$ = 26.2 Hz, C=O), 161.0 (C), 164.0 (N—C=O), 167.0 and 169.1 (2C=O). MS, *m/z* (%): 333 (M^+, 17), 342 (10), 326 (45), 302 (25), 214 (15), 169 (68), 57 (100), 41 (65). Anal. Calcd for $C_{17}H_{22}FN_3O_6$ (383.37): C, 53.26; H, 5.78; N, 10.96. Found: C, 54.20; H, 5.65; N, 11.20%.

Dimethyl-7-bromo-2-(cyclohexylamino)-8-oxo-2H,8H-pyrimido [2,1-b][1,3]oxazine-3,4-dicarboxylate (5i, $C_{17}H_{20}BrN_3O_6$). White powder, mp 387–393°C, 0.60 g, yield 78%; IR (KBr) (υ_{max}/cm^{-1}): NH 3367, C=O 1699, 1679, and 1662. ^{1}H-NMR (300.1 MHz, $CDCl_3$): δ 1.34–2.03 [10H, m, $CH(CH_2)_5$], 3.73 and 3.78 (6H, 2s, $2CH_3$), 3.92–3.96 (1H, m, NHC*H*), 6.68 (1H, s, NHC*H*O), 7.86 (1H, s, NCH), 9.44 (1H, br. s, NH).^{13}C-NMR (75.5 MHz, $CDCl_3$): 23.7, δ 25.7, 26.1, 28.6, and 32.0 ($5CH_2$), 52.0 and 53.4 ($2OCH_3$), 57.4 (NHCH), 127.3 (CBr), 96.2 (NHCHO), 137.0 and 150.1 (2C), 158.1 (N=C—O), 159.3, 167.3, and 169.8 (3C=O). MS, *m/z* (%): 442 (M^+, 6), 444 [M^++2, 5.7)], 384 (20), 252 (100), 192 (18), 170 (94), 149 (12), 138 (35), 83 (58), 55 (53), 41 (23). Anal. Calcd for $C_{17}H_{20}BrN_3O_6$ (442.26): C, 46.17; H, 4.56; N, 9.50. Found: C, 47.12; H, 4.38; N, 9.98%.

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REFERENCES AND NOTES

[1] (a) Zhu, J.; Bienaymé, H., Eds. Multicomponent Reactions; Wiley-VCH: Weinheim, 2005; (b) Dömling, A.; Ugi, I. Angew Chem Int Ed 2000, 39, 3169; (c) Simon, C.; Constantieux, T.; Rodriguez, J. Eur J Org Chem 2004, 24, 4957; (d) Cui, S. L.; Lin, X. F.; Wang, Y. G. J Org Chem 2005, 70, 2866.

[2] (a) Winterfeldt, E.; Schumann, D.; Dillinger, H. J. Chem Ber 1969, 102, 1656; (b) Dillinger, H. J.; Fengler, G.; Schumann, D.; Winterfeldt, E. Tetrahedron 1974, 30, 2553; (c) Junjappa, H.; Saxena, M. K.; Ramaiah, D.; Lohray, B. B.; Rath, N. P.; George, M. V. J Org Chem 1998, 63, 9801; (d) Nair, V.; Rajesh, C.; Vinod, A. U.; Bindu, S.; Sreekanth, A. R.; Mathen, J. S.; Balagopal, L. Acc Chem Res 2003, 36, 899.

[3] Yavari, I.; Nasiri, F.; Moradi, L.; Djahaniani, H. Tetrahedron Lett 2004, 45, 7099.

[4] (a) Yavari, I.; Alizadeh, A.; Anary-Abbasinejad, M.; Bijanzadeh, H. R. Tetrahedron 2003, 59, 6083; (b) Baharfar, R.; Hossein nia, R.; Baghbanian, S. M. Lett Org Chem 2008, 5, 128.

[5] Swinbourne, J. F.; Hunt, H. J.; Klinkert, G. Adv Heterocycl Chem 1987, 23, 103.

[6] (a) Haneishi, T.; Okazaki, T.; Hata, T.; Tamura, C.; Nomura, M.; Naito, A.; Seki, I.; Arai, M. J Antibiot 1971, 24, 797; (b) Johnson. P. Y.; Silver, R. J Heterocycl Chem 1973, 10, 1029; (c) Mosher, H. S.; Frankel, M. B.; Gregory, M. J Am Chem Soc 1953, 75, 5326; (d) Khumtaveeporn, K.; Alper, H. J Org Chem 1995, 60, 8142.

[7] (a) Sainsbury, M. In Comprehensive Heterocyclic Chemistry; Boulton, A. J., Mckillop A., Eds.; Pergamon Press: Canada, 1984; Vol. 3, Part 2B, p 995; (b) Kato, T.; Katagiri, N.; Yamamoto, Y. Heterocycles 1980, 14, 1333.

[8] (a) Baharfar, R.; Vahdat, S. M.; Baghbanian, S. M. Acta Crystallogr Sect E 2008, E64, o1203; (b) Baharfar, R.; Asghari, S.; Hamedaninejad, A.; Abbasi, A.; Ostadzadeh, A.; Bijanzadeh, H. R. Lett Org Chem 2007, 4, 429.

[9] Jang, Y. H.; Sowers, L. C.; Cagin, T.; Goddard, W. A. J Phys Chem A 2001, 105, 274.

[10] (a) Gondela, A.; Walczak, K. Tetrahedron Lett 2006, 47, 4653; (b) Soltani Rad, M. N.; Khalafi-Nezhad, A.; Behrouz, S.; Faghihi, M. A.; Zare, A.; Parhami, A. Tetrahedron 2008, 64, 1778.

[11] (a) Ugi, I. Isonitrile Chemistry; Academic Press: New York, London, 1971; (b) Ugi, I. Angew Chem Int Ed Engl 1982, 21, 810.