Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron
Tetrahedron 63 (2007) 11135–11140

A new, one-pot, three-component synthesis of 4*H*-pyrido[1,2-*a*]-pyrimidines, 4*H*-pyrimido[1,2-*a*]pyrimidines, and 4*H*-pyrazino[1,2-*a*]pyrimidines

Mehdi Adib,[a,*] Mohammad Hosein Sayahi,[a] Hakimeh Ziyadi,[a] Hamid Reza Bijanzadeh[b] and Long-Guan Zhu[c]

[a]*School of Chemistry, University College of Science, University of Tehran, PO Box 14155-6455, Tehran, Iran*
[b]*Department of Chemistry, Tarbiat Modarres University, PO Box 14115-175, Tehran, Iran*
[c]*Chemistry Department, Zhejiang University, Hangzhou 310027, PR China*

Received 11 May 2007; revised 9 July 2007; accepted 8 August 2007
Available online 14 August 2007

Abstract—A new, one-pot and three-component synthesis of 4*H*-pyrido[1,2-*a*]pyrimidines, 4*H*-pyrimido[1,2-*a*]pyrimidines, and 4*H*-pyrazino[1,2-*a*]pyrimidines is described. The reactive 1:1 zwitterionic intermediate, formed by the addition of isocyanides to dialkyl acetylenedicarboxylates, was trapped by *N*-(2-heteroaryl)amides to yield a ketenimine intermediate, which was cyclized and then rearranged under the reaction conditions to afford the title compounds under mild reaction conditions in good yields. Single-crystal X-ray analysis conclusively confirms the structure of the obtained bridgehead bicyclic 6–6 heterocyclic compounds.

1. Introduction

Multi-component reactions (MCRs) have become a significant part of today's arsenal of methods in combinatorial chemistry.[1] MCRs, leading to interesting heterocyclic scaffolds, are particularly useful for the construction of diverse chemical libraries of 'drug-like' molecules. The isocyanide-based MCRs are especially important in this area.[1b,c]

Bridgehead nitrogen heterocycles are of interest because they constitute an important class of natural and non-natural products, many of which exhibit useful biological activity. The interest in bicyclic 6–6 systems stems from the occurrence of saturated and partially saturated pyrido[1,2-*a*]pyrimidines, pyrimido[1,2-*a*]pyrimidines, and pyrazino[1,2-*a*]pyrimidines in many biologically active compounds and natural products.[2–6]

To date, the most common synthetic methods reported for the preparation of pyrido[1,2-*a*]pyrimidine ring systems involve: (i) transformation of an existing heterocycle and (ii) cyclizations, classified on the basis of the number of ring atoms in each of the components being cyclized.[2,4]

There are several methods reported in the literature for the preparation of pyrimido[1,2-*a*]pyrimidine and pyrazino[1,2-*a*]pyrimidine ring system. The most common synthetic routes involve [3+3] ring closure of 2-aminopyrimidines and 2-aminopyrazines with a variety of bifunctional electrophiles.[3,7,8]

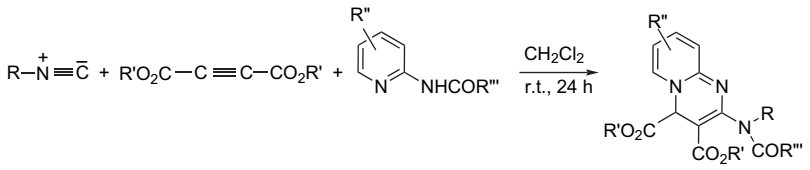
The diverse pharmacological activities of the three fused bicyclic 6–6 heterocycles encouraged us to develop a concise synthetic route to these heterocyclic compounds.

2. Results and discussion

As part of our current studies on the design of new routes for the preparation of biologically active heterocyclic compounds,[9] we report herein a simple synthesis of functionalized 4*H*-pyrido[1,2-*a*]pyrimidines,[4a] 4*H*-pyrimido[1,2-*a*]-pyrimidines, and 4*H*-pyrazino[1,2-*a*]pyrimidines using simple starting materials from [1+2+3] atom fragments by formation of three bonds. Thus, a mixture of an isocyanide **1**, a dialkyl acetylenedicarboxylate **2**, and an *N*-(2-heteroaryl)amide **3** or **5** undergoes a smooth 1:1:1 addition reaction in dry CH_2Cl_2 at ambient temperature to produce 2-amino-4*H*-pyrido[1,2-*a*]pyrimidine-3,4-dicarboxylates **4a–j** in 83–92% yields (Scheme 1), 2-amino-4*H*-pyrimido[1,2-

Keywords: 4*H*-Pyrido[1,2-*a*]pyrimidines; 4*H*-Pyrimido[1,2-*a*]pyrimidines; 4*H*-Pyrazino[1,2-*a*]pyrimidines; Three-component synthesis; Acetylenic esters; Isocyanides.
* Corresponding author. Tel./fax: +98 21 66495291; e-mail: madib@khayam.ut.ac.ir

0040–4020/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2007.08.024



1 2 3 4

4	R	R'	R''	R'''	% Yield
a	Cyclohexyl	Me	H	CO_2Et	92
b	Cyclohexyl	Et	H	CO_2Et	88
c	Cyclohexyl	Me	7-Me	CO_2Et	90
d	Cyclohexyl	Et	7-Me	CO_2Et	85
e	Cyclohexyl	Me	H	OEt	83
f	^{t}Bu	Me	H	CO_2Et	89
g	^{t}Bu	Et	H	CO_2Et	85

Scheme 1.

a]pyrimidine-3,4-dicarboxylates, and 2-amino-4*H*-pyrazino[1,2-*a*]pyrimidine-3,4-dicarboxylates **6a–j** in 79–94% yields (Scheme 2).

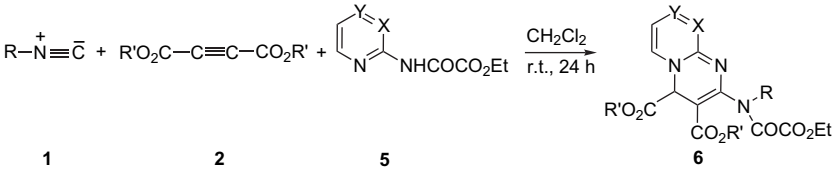
The one-pot three-component condensation reactions were carried out by first mixing acetylenic ester **2** and *N*-(2-heteroaryl)amide **3** or **5** in dry CH_2Cl_2. Then, a solution of isocyanide **1** in dry CH_2Cl_2 was added to the reaction mixture. The reaction proceeded smoothly at ambient temperature and was complete within 24 h to afford the corresponding pyrido[1,2-*a*]pyrimidines **4** or azino[1,2-*a*]pyrimidines **6**. The ^{1}H NMR spectra of the crude products clearly indicated the formation of fused system **4** or **6**. Any product other than **4** or **6** could not be detected by NMR spectroscopy.

The structures of the pyrido[1,2-*a*]pyrimidines **4a–g** were confirmed by IR, ^{1}H, and ^{13}C NMR spectroscopy, mass spectrometry, and elemental analysis. The mass spectrum of **4a** displayed the molecular ion (M^+) peak at *m/z* 445, which was consistent with the 1:1:1 adduct of cyclohexyl isocyanide, dimethyl acetylenedicarboxylate, and ethyl 2-oxo-2-(2-pyridylamino)acetate. The ^{1}H NMR spectrum of **4a** exhibited three sharp singlets, arising from the two CH_3O (δ 3.64 and 3.69 ppm) and methine (δ 6.01 ppm) groups along with the characteristic signals with appropriate chemical shifts and coupling constants for the 16 protons of the ethoxy and cyclohexyl functions, as well as the characteristic multiplets for the four protons of the diene moiety of the pyridine ring. The ^{1}H-decoupled ^{13}C NMR spectrum of **4a** showed 22 distinct resonances, in agreement with the proposed structure.

The isolated azino[1,2-*a*]pyrimidines **6a–g** were characterized on the basis of their elemental analyses and IR, ^{1}H NMR, and ^{13}C NMR spectra. The nature of these compounds as 1:1:1 adducts was apparent from the mass spectra, which displayed molecular ion peaks at the appropriate *m/z* values. The ^{1}H NMR spectrum of **6a** consisted of multiplet signals for the 11 protons of the cyclohexyl ring and the five protons of the ethoxy function (δ 1.04–2.15 and 4.04–4.26 ppm). Three single sharp lines were observed for the two CH_3O (δ 3.70 and 3.74 ppm) and methine (δ 6.08 ppm) groups. Three characteristic doublet of doublets (δ 6.87, 7.90, and 8.76 ppm; J=6.6, 4.0, and 2.1 Hz) were seen for the three mutually coupling CHs in positions 6, 7, and 8 of the bicyclic ring. The ^{1}H-decoupled ^{13}C NMR spectrum of **6a** showed 21 distinct resonances, in agreement with the suggested structure. Partial assignments of these resonances are given in Section 4.

Single-crystal X-ray analysis of **4a** conclusively confirmed the structure of the isolated products. An ORTEP diagram of **4a** is shown in Figure 1.[10]

A mechanistic rationalization for this reaction is provided in Scheme 3 (exemplified by **4**). On the basis of the well-established chemistry of isocyanides,[1b,c,11] it is reasonable to assume that the pyrido[1,2-*a*]pyrimidines **4** result from initial addition of isocyanide to acetylenic ester and subsequent protonation of the 1:1 zwitterionic adduct **7** by *N*-(2-pyridyl)-amide **3**, followed by conjugate addition of anion **9** from the pyridine nitrogen to the α,β-unsaturated nitrilium ion **8** to



1 2 5 6

6	R	R'	X	Y	% Yield
a	Cyclohexyl	Me	N	CH	94
b	Cyclohexyl	Et	N	CH	90
c	^{t}Bu	Me	N	CH	89
d	^{t}Bu	Et	N	CH	83
e	1,1,3,3-tetramethylbutyl	Et	N	CH	79
f	Cyclohexyl	Me	CH	N	91
g	Cyclohexyl	Et	CH	N	89

Scheme 2.

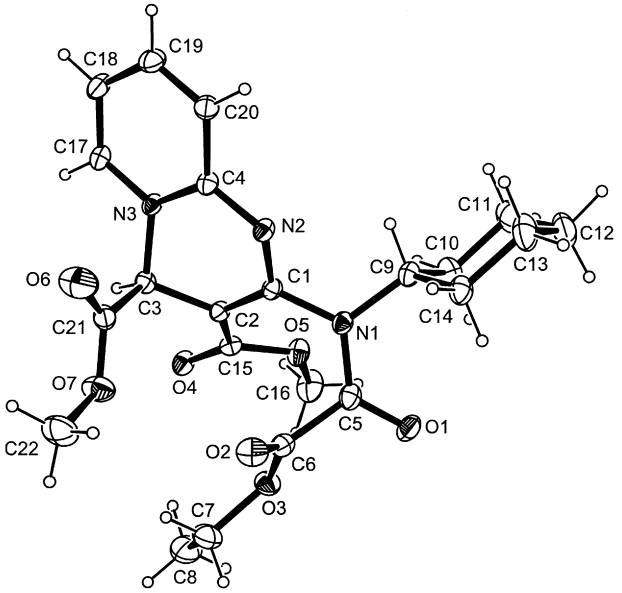
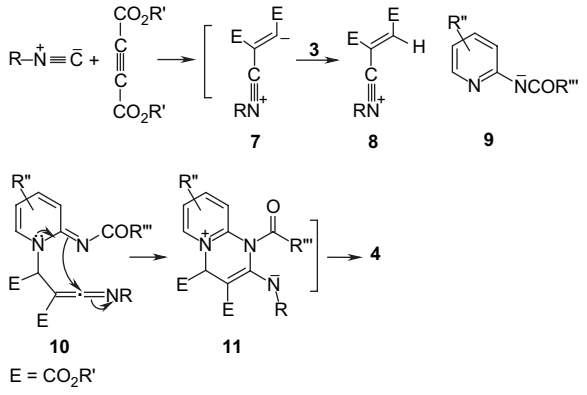


Figure 1. Molecular structure of **4a**, with 50% probability displacement ellipsoids, H atoms with arbitrary radii.

form ketenimine intermediate **10**. Ketenimine may undergo intramolecular cyclization to bicyclic zwitterion **11**, which undergo rearrangement to afford the fused heterocyclic system **4**.



Scheme 3.

3. Conclusion

In summary, we have developed a new, one-pot, and three-component synthesis of 2-amino-4*H*-pyrido[1,2-*a*]pyrimidines-3,4-dicarboxylates, 2-amino-4*H*-pyrimido[1,2-*a*]-pyrimidine-3,4-dicarboxylates, and 2-amino-4*H*-pyrazino-[1,2-*a*]pyrimidine-3,4-dicarboxylates of potential synthetic and pharmacological interest. The good yields of the products, the mild reaction conditions, and the use of simple starting materials are the main advantages of this method. The reactions were performed under neutral conditions and the substances were mixed without any activation or modification. The simplicity of this method makes it an interesting alternative to other approaches.

4. Experimental

4.1. General

Dimethyl- and diethyl acetylenedicarboxylates, *tert*-butyl-, cyclohexyl- and 1,1,3,3-tetramethylbutyl isocyanides, 2-aminopyridines, 2-aminopyrimidine, and 2-aminopyrazine, ethyl chloroglyoxalate, and ethyl chloroformate were obtained from Merck (Germany) and Fluka (Switzerland) and were used without further purification. *N*-(2-Heteroaryl)-amides **3** and **5** were prepared according to the procedure.[12] 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 and ^{13}C NMR spectra were measured with Bruker DRX-500 AVANCE (at 500.1 and 125.8 MHz) and Bruker DRX-300 (at 300.1 and 75.5 MHz) spectrometers using $CDCl_3$ solvent with TMS as an internal standard. IR spectra were recorded on a Shimadzu IR-460 spectrometer. Chromatography columns were prepared from Merck silica gel 60 mesh.

4.2. General procedure

To a magnetically stirred solution of the appropriate *N*-(2-heteroaryl)amide, **3** or **5** (1 mmol) and the appropriate acetylenic ester (1 mmol) in dry CH_2Cl_2 (6 mL) was added dropwise a solution of the appropriate isocyanide (1 mmol) in dry CH_2Cl_2 (2 mL) at 25 °C over 10 min. The reaction mixture was then stirred for 24 h. The solvent was removed and the residue was purified by column chromatography using hexane–ethyl acetate (1:2) as eluent. The solvent was removed and the product was crystallized from 1:1 hexane–ethyl acetate.

4.2.1. Dimethyl 2-[cyclohexyl(2-ethoxy-2-oxoacetyl)-amino]-4*H*-pyrido[1,2-*a*]pyrimidine-3,4-dicarboxylate (4a). Yellow crystals, mp 167–169 °C, yield: 0.41 g, 92%. IR (KBr) (ν_{max}/cm^{-1}): 1742, 1730, 1672, and 1640 (C═O), 1564, 1487, 1396, 1330, 1219, 1146, 1094, 989, 770. MS, *m*/*z* (%): 445 (M$^+$, 6), 417 (4), 386 (98), 372 (13), 344 (18), 304 (28), 290 (27), 230 (90), 205 (100), 170 (22), 78 (21), 55 (16). Anal. Calcd for $C_{22}H_{27}N_3O_7$ (445.47): C, 59.32; H, 6.11; N, 9.43. Found: C, 59.1; H, 6.3; N, 9.2%. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 1.02–2.13 [3H, t, J=7.0 Hz, OCH_2CH_3; 10H, m, $CH(CH_2)_5$], 3.64 and 3.69 (6H, 2s, $2OCH_3$), 3.99–4.25 [3H, m, OCH_2CH_3 and $NCH(CH_2)_5$], 6.01 (1H, s, NCH), 6.76 (1H, dd, J=6.6, 6.2 Hz, CH), 7.13 (1H, d, J=8.3 Hz, CH), 7.38 (1H, d, J=6.2 Hz, CH), 7.56 (1H, dd, J=8.3, 6.6 Hz, CH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 13.8 (OCH_2CH_3), 25.7, 26.1, 26.1, 28.6, and 32.0 ($5CH_2$), 51.6 and 52.9 ($2OCH_3$), 56.8 [$NCH(CH_2)_5$], 61.4 (NCH), 62.3 (OCH_2), 87.3 (N_2C═C), 114.5, 123.8, 137.0, and 139.1 (4CH), 152.7 and 153.5 (2C), 161.9, 162.4, 164.8, and 168.2 (4C═O).

4.2.2. Diethyl 2-[cyclohexyl(2-ethoxy-2-oxoacetyl)-amino]-4*H*-pyrido[1,2-*a*]pyrimidine-3,4-dicarboxylate (4b). Yellow crystals, mp 152 °C, yield: 0.42 g, 88%. IR (KBr) (ν_{max}/cm^{-1}): 1744, 1729, 1678, and 1639 (C═O), 1618, 1566, 1481, 1404, 1335, 1234, 1211, 1138, 1094, 1030, 808, 770. MS, *m*/*z* (%): 473 (M$^+$, 8), 400 (100), 383

(32), 354 (30), 337 (45), 318 (47), 272 (31), 255 (80), 227 (75), 199 (40), 172 (25), 121 (31), 78 (65), 55 (20). Anal. Calcd for $C_{24}H_{31}N_3O_7$ (473.53): C, 60.88; H, 6.60; N, 8.87. Found: C, 60.7; H, 6.8; N, 8.6%. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 1.00–2.09 [9H, 3t, J=7.1 Hz, 3OCH$_2$CH_3; 10H, m, CH(CH_2)$_5$], 3.95–4.26 [7H, m, 3OCH_2CH$_3$ and NCH(CH$_2$)$_5$], 5.97 (1H, s, NCH), 6.70 (1H, dd, J=6.7, 6.5 Hz, CH), 7.08 (1H, d, J=8.8 Hz, CH), 7.37 (1H, d, J=6.5 Hz, CH), 7.50 (1H, dd, J=8.8, 6.7 Hz, CH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 13.7, 13.8, and 14.1 (3OCH$_2$$CH_3$), 25.5, 25.9, 26.0, 28.4, and 32.0 (5CH$_2$), 56.4 [NCH(CH$_2$)$_5$], 60.5 (OCH$_2$), 61.4 (NCH), 62.1, and 62.2 (2OCH$_2$), 88.6 (N$_2$C=C), 113.9, 123.6, 136.9, and 138.6 (4CH), 152.5 and 152.8 (2C), 161.6, 162.2, 164.3, and 167.6 (4C=O).

4.2.3. Dimethyl 2-[cyclohexyl(2-ethoxy-2-oxoacetyl)-amino]-7-methyl-4*H*-pyrido[1,2-*a*]pyrimidine-3,4-dicarboxylate (4c). Yellow crystals, mp 155–157 °C, yield: 0.41 g, 90%. IR (KBr) (ν_{max}/cm^{-1}): 1743, 1730, 1677, and 1643 (C=O), 1567, 1490, 1433, 1390, 1220, 1140, 1096, 1012, 970. MS, *m*/*z* (%): 459 (M$^+$, 7), 400 (75), 372 (18), 318 (25), 258 (33), 233 (100), 92 (22), 57 (9). Anal. Calcd for $C_{23}H_{29}N_3O_7$ (459.50): C, 60.12; H, 6.36; N, 9.14. Found: C, 60.1; H, 6.4; N, 9.1%. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 1.02–2.13 [3H, t, J=7.1 Hz, OCH$_2$CH_3; 10H, m, CH(CH_2)$_5$], 2.21 (3H, s, CH$_3$), 3.66 and 3.69 (6H, 2 s, 2OCH$_3$), 4.05–4.25 [3H, m, OCH_2CH$_3$ and NCH(CH$_2$)$_5$], 5.96 (1H, s, NCH), 7.09 (1H, d, J=8.7 Hz, CH), 7.14 (1H, s, CH), 7.43 (1H, d, J=8.7 Hz, CH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 13.8 (OCH$_2$$CH_3$), 17.4 (CH$_3$), 25.7, 26.0, 26.1, 28.5, and 32.0 (5CH$_2$), 51.5 and 52.8 (2OCH$_3$), 56.7 [NCH(CH$_2$)$_5$], 61.3 (NCH), 62.5 (OCH$_2$), 86.3 (N$_2$C=C), 123.5 (CH), 124.6 (C), 134.5 and 141.5 (2CH), 151.5 and 153.8 (2C), 161.9, 162.4, 164.8, and 168.3 (4C=O).

4.2.4. Diethyl 2-[cyclohexyl(2-ethoxy-2-oxoacetyl)-amino]-7-methyl-4*H*-pyrido[1,2-*a*]pyrimidine-3,4-dicarboxylate (4d). Yellow crystals, mp 147 °C, yield: 0.41 g, 85%. IR (KBr) (ν_{max}/cm^{-1}): 1744, 1728, 1674, and 1641 (C=O), 1568, 1489, 1421, 1337, 1229, 1130, 1096, 1032, 847, 623. MS, *m*/*z* (%): 487 (M$^+$, 5), 414 (84), 386 (24), 332 (31), 258 (38), 233 (100), 205 (22), 186 (10), 92 (17), 55 (8). Anal. Calcd for $C_{25}H_{33}N_3O_7$ (487.55): C, 61.59; H, 6.82; N, 8.62. Found: C, 61.6; H, 6.9; N, 8.5%. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 0.96–2.02 [9H, 3t, J=7.1 Hz, 3OCH$_2$CH_3; 10H, m, CH(CH_2)$_5$], 2.15 (3H, s, CH$_3$), 3.90–4.20 [7H, m, 3OCH_2CH$_3$ and NCH(CH$_2$)$_5$], 5.91 (1H, s, NCH), 7.01 (1H, d, J=8.8 Hz, CH), 7.17 (1H, s, CH), 7.37 (1H, d, J=8.8 Hz, CH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 13.6, 13.8, and 14.0 (3OCH$_2$$CH_3$), 17.2 (CH$_3$), 25.5, 25.8, 25.9, 28.3, and 32.0 (5CH$_2$), 56.3 [NCH(CH$_2$)$_5$], 60.3 (OCH$_2$), 61.2 (NCH), 62.0 and 62.2 (2OCH$_2$), 87.6 (N$_2$C=C), 123.1 (CH), 124.3 (C), 134.6 and 141.4 (2CH), 151.3 and 153.0 (2C), 161.6, 162.2, 164.3, and 167.8 (4C=O).

4.2.5. Dimethyl 2-[cyclohexyl(ethoxycarbonyl)amino]-4*H*-pyrido[1,2-*a*]pyrimidine-3,4-dicarboxylate (4e). Yellow crystals, mp 158–159 °C, yield: 0.35 g, 83%. IR (KBr) (ν_{max}/cm^{-1}): 1749, 1729, 1720, 1668, and 1637 (C=O), 1625, 1568, 1493, 1393, 1331, 1219, 1144, 1097. MS, *m*/*z* (%): 417 (M$^+$, 3), 386 (65), 344 (11), 304 (17), 290 (17), 230 (100), 205 (71), 170 (16), 78 (17), 55 (9). Anal. Calcd for $C_{21}H_{27}N_3O_6$ (417.46): C, 60.42; H, 6.52; N, 10.07. Found: C, 60.4; H, 6.5; N, 9.9%. ^{1}H NMR (300.1 MHz, $CDCl_3$): δ 1.02–2.15 [3H, t, J=7.1 Hz, OCH$_2$CH_3; 10H, m, CH(CH_2)$_5$], 3.68 and 3.72 (6H, 2s, 2OCH$_3$), 3.95–4.30 [3H, m, OCH_2CH$_3$ and NCH(CH$_2$)$_5$], 6.03 (1H, s, NCH), 6.80 (1H, dd, J=6.7, 6.4 Hz, CH), 7.18 (1H, d, J=8.8 Hz, CH), 7.39 (1H, d, J=6.4 Hz, CH), 7.59 (1H, dd, J=8.8, 6.7 Hz, CH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 13.9 (OCH$_2$$CH_3$), 25.6, 26.0, 26.1, 28.5, and 32.0 (5CH$_2$), 51.8 and 53.0 (2OCH$_3$), 56.8 [NCH(CH$_2$)$_5$], 61.5 (NCH), 62.3 (OCH$_2$), 87.3 (N$_2$C=C), 114.6, 123.8, 136.9, and 139.2 (4CH), 152.6 and 161.9 (2C), 162.3, 164.8, and 168.1 (3C=O).

4.2.6. Dimethyl 2-[*tert*-butyl(2-ethoxy-2-oxoacetyl)-amino]-4*H*-pyrido[1,2-*a*]pyrimidine-3,4-dicarboxylate (4f). Yellow crystals, mp 160 °C, yield: 0.37 g, 89%. IR (KBr) (ν_{max}/cm^{-1}): 1745, 1729, 1684, and 1659 (C=O), 1632, 1566, 1490, 1430, 1391, 1323, 1221, 1194, 1138, 1099, 1010, 959, 771. MS, *m*/*z* (%): 419 (M$^+$, 3), 360 (20), 304 (97), 290 (17), 230 (100), 205 (20), 170 (12), 78 (18), 57 (7). Anal. Calcd for $C_{20}H_{25}N_3O_7$ (419.43): C, 57.27; H, 6.01; N, 10.02. Found: C, 57.1; H, 6.1; N, 10.1%. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 1.20 (3H, t, J=7.1 Hz, OCH$_2$CH_3), 1.43 [9H, s, C(CH$_3$)$_3$], 3.61 and 3.69 (6H, 2s, 2OCH$_3$), 4.05 and 4.17 (2H, 2dq, ABX_3 system, ^2J=10.6 Hz and ^3J=7.1 Hz, OC$H_A$$H_BCH_3$), 5.99 (1H, s, NCH), 6.71 (1H, dd, J=6.7, 6.1 Hz, CH), 7.05 (1H, d, J=8.9 Hz, CH), 7.36 (1H, d, J=6.1 Hz, CH), 7.50 (1H, dd, J=8.9, 6.7 Hz, CH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 13.7 (OCH$_2$$CH_3$), 28.0 [C($CH_3$)$_3$], 51.4 and 52.8 (2OCH$_3$), 60.3 [$C$(CH$_3$)$_3$], 61.0 (NCH), 62.1 (OCH$_2$), 91.7 (N$_2$C=$C$), 114.2, 123.6, 136.8, and 138.9 (4CH), 152.3 and 152.7 (2C), 161.4, 162.2, 164.5, and 168.0 (4C=O).

4.2.7. Diethyl 2-[*tert*-butyl(2-ethoxy-2-oxoacetyl)amino]-4*H*-pyrido[1,2-*a*]pyrimidine-3,4-dicarboxylate (4g). Yellow crystals, mp 110–111 °C, yield: 0.38 g, 85%. IR (KBr) (ν_{max}/cm^{-1}): 1738, 1675, 1657, and 1640 (C=O), 1574, 1492, 1393, 1319, 1232, 1193, 1142, 1093, 1024, 964, 773. MS, *m*/*z* (%): 447 (M$^+$, 2), 374 (22), 318 (100), 244 (43), 216 (24), 172 (13), 78 (17), 57 (8). Anal. Calcd for $C_{22}H_{29}N_3O_7$ (447.49): C, 59.05; H, 6.53; N, 9.39. Found: C, 59.0; H, 6.6; N, 9.4%. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 1.11, 1.21, and 1.28 (9H, 3t, J=7.1 Hz, 3OCH$_2$CH_3), 1.45 [9H, s, C(CH$_3$)$_3$], 4.00–4.30 (6H, m, 3OCH$_2$), 5.96 (1H, s, NCH), 6.66 (1H, dd, J=6.7, 6.5 Hz, CH), 7.04 (1H, d, J=8.9 Hz, CH), 7.32 (1H, d, J=6.5 Hz, CH), 7.47 (1H, dd, J=8.9, 6.7 Hz, CH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 13.7, 13.8, and 14.2 (3OCH$_2$CH_3), 28.1 [C(CH$_3$)$_3$], 60.3 [C(CH$_3$)$_3$], 60.7 (OCH$_2$), 61.1 (NCH), 62.2 and 62.3 (2OCH$_2$), 93.4 (N$_2$C=C), 113.5, 123.5, 136.7, and 138.4 (4CH), 151.7 and 152.2 (2C), 161.4, 162.1, 164.3, and 167.6 (4C=O).

4.2.8. Dimethyl 2-[cyclohexyl(2-ethoxy-2-oxoacetyl)-amino]-4*H*-pyrido[1,2-*a*]pyrimidine-3,4-dicarboxylate (6a). Yellow crystals, mp 189 °C, yield: 0.42 g, 94%. IR (KBr) (ν_{max}/cm^{-1}): 1744, 1721, 1691, and 1676 (C=O), 1620, 1568, 1491, 1412, 1325, 1225, 1121, 1096, 1012, 805. MS, *m*/*z* (%): 446 (M$^+$, 10), 387 (60), 373 (23),

345 (35), 305 (48), 291 (35), 259 (20), 231 (100), 206 (83), 171 (15), 79 (30), 55 (23). Anal. Calcd for $C_{21}H_{26}N_4O_7$ (446.46): C, 56.50; H, 5.87; N, 12.55. Found: C, 56.4; H, 5.9; N, 12.4%. ^{1}H NMR (300.1 MHz, $CDCl_3$): δ 1.04–2.15 [3H, t, J=7.1 Hz, OCH_2CH_3; 10H, m, $CH(CH_2)_5$], 3.70 and 3.74 (6H, 2s, $2OCH_3$), 4.04–4.26 [3H, m, OCH_2CH_3 and $NCH(CH_2)_5$], 6.08 (1H, s, NCH), 6.87 (1H, dd, J=6.6, 4.0 Hz, CH), 7.90 (1H, dd, J=6.6, 2.1 Hz, CH), 8.76 (1H, dd, J=4.0, 2.1 Hz, CH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 13.8 (OCH_2CH_3), 25.3, 26.0, 26.1, 28.6, and 31.4 ($5CH_2$), 52.0 and 53.3 ($2OCH_3$), 57.5 [$NCH(CH_2)_5$], 61.6 (NCH), 62.3 (OCH_2), 90.2 ($N_2C{=}C$), 111.3 and 146.6 (2CH), 152.8 and 153.3 (2C), 161.6 and 162.1 (2C=O), 163.9 (CH), 164.3 and 167.8 (2C=O).

4.2.9. Diethyl 2-[cyclohexyl(2-ethoxy-2-oxoacetyl)-amino]-4*H*-pyrimido[1,2-*a*]pyrimidine-3,4-dicarboxylate (6b). Yellow crystals, mp 156 °C, yield: 0.43 g, 90%. IR (KBr) (ν_{max}/cm^{-1}): 1740, 1684, and 1664 (C=O), 1620, 1566, 1499, 1414, 1304, 1221, 1126, 1016, 804. MS, *m*/*z* (%): 474 (M^+, 6), 401 (97), 373 (21), 347 (8), 319 (64), 245 (57), 220 (100), 173 (13), 149 (15), 79 (21), 55 (20). Anal. Calcd for $C_{23}H_{30}N_4O_7$ (474.51): C, 58.22; H, 6.37; N, 11.81. Found: C, 58.2; H, 6.5; N, 11.6%. ^{1}H NMR (300.1 MHz, $CDCl_3$): δ 1.02–2.16 [9H, 3t, J=7.1 Hz, $3OCH_2CH_3$; 10H, m, $CH(CH_2)_5$], 4.02–4.25 [7H, m, $3OCH_2CH_3$ and $NCH(CH_2)_5$], 6.02 (1H, s, NCH), 6.80 (1H, dd, J=6.6, 4.0 Hz, CH), 7.79 (1H, dd, J=6.6, 2.1 Hz, CH), 8.73 (1H, dd, J=4.0, 2.1 Hz, CH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 12.4, 12.5, and 12.7 ($3OCH_2CH_3$), 23.9, 24.5, 24.6, 27.1, and 30.1 ($5CH_2$), 55.8 [$NCH(CH_2)_5$], 59.8 (OCH_2), 60.2 (NCH), 60.9 and 61.3 ($2OCH_2$), 89.8 ($N_2C{=}C$), 109.2 and 144.9 (2CH), 151.3 and 151.6 (2C), 160.1 and 160.6 (2C=O), 162.2 (CH), 162.7 and 165.9 (2C=O).

4.2.10. Dimethyl 2-[*tert*-butyl(2-ethoxy-2-oxoacetyl)-amino]-4*H*-pyrimido[1,2-*a*]pyrimidine-3,4-dicarboxylate (6c). Yellow crystals, mp 186 °C, yield: 0.37 g, 89%. IR (KBr) (ν_{max}/cm^{-1}): 1748, 1740, 1718, and 1668 (C=O), 1626, 1600, 1512, 1431, 1402, 1382, 1362, 1308, 1282, 1254, 1221, 1126, 1090, 943, 790. MS, *m*/*z* (%): 420 (M^+, 2), 363 (11), 347 (9), 305 (100), 291 (40), 259 (16), 231 (84), 171 (13), 79 (16), 57 (12). Anal. Calcd for $C_{19}H_{24}N_4O_7$ (420.42): C, 54.28; H, 5.75; N, 13.33. Found: C, 54.3; H, 5.8; N, 13.3%. ^{1}H NMR (300.1 MHz, $CDCl_3$): δ 1.26 (3H, t, J=7.1 Hz, OCH_2CH_3), 1.50 [9H, s, $C(CH_3)_3$], 3.69 and 3.78 (6H, 2s, $2OCH_3$), 4.12 and 4.23 (2H, 2dq, ABX_3 system, ^2J=10.6 Hz and ^3J=7.1 Hz, $OCH_AH_BCH_3$), 6.10 (1H, s, NCH), 6.82 (1H, dd, J=6.6, 4.0 Hz, CH), 7.90 (1H, dd, J=6.6, 2.1 Hz, CH), 8.72 (1H, dd, J=4.0, 2.1 Hz, CH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 13.9 (OCH_2CH_3), 28.1 [$C(CH_3)_3$], 51.9 and 53.3 ($2OCH_3$), 60.7 [$C(CH_3)_3$], 61.3 (NCH), 62.2 (OCH_2), 95.4 ($N_2C{=}C$), 111.0 and 146.5 (2CH), 151.1 and 152.5 (2C), 161.4 and 162.1 (2C=O), 163.9 (CH), 164.3 and 167.8 (2C=O).

4.2.11. Diethyl 2-[*tert*-butyl(2-ethoxy-2-oxoacetyl)-amino]-4*H*-pyrimido[1,2-*a*]pyrimidine-3,4-dicarboxylate (6d). Yellow crystals, mp 138 °C, yield: 0.37 g, 83%. IR (KBr) (ν_{max}/cm^{-1}): 1736, 1727, 1681, and 1666 (C=O), 1620, 1568, 1487, 1382, 1319, 1294, 1261, 1219, 1161, 1118, 1092, 1013, 968, 700. MS, *m*/*z* (%): 448 (M^+, 4), 391 (13), 375 (29), 347 (8), 319 (100), 273 (12), 245 (89), 217 (37), 173 (14), 130 (12), 79 (19), 57 (8). Anal. Calcd for $C_{21}H_{28}N_4O_7$ (448.48): C, 56.24; H, 6.29; N, 12.49. Found: C, 56.0, H, 6.3; N, 12.4%. ^{1}H NMR (300.1 MHz, $CDCl_3$): δ 1.03, 1.18, and 1.32 (9H, 3t, J=7.1 Hz, $3OCH_2CH_3$), 1.59 [9H, s, $C(CH_3)_3$], 4.03–4.37 (6H, m, $3OCH_2CH_3$), 5.96 (1H, s, NCH), 6.69 (1H, dd, J=6.6, 4.0 Hz, CH), 7.79 (1H, dd, J=6.6, 2.2 Hz, CH), 8.61 (1H, dd, J=4.0, 2.2 Hz, CH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 13.7, 13.9, and 14.4 ($3OCH_2CH_3$), 28.1 [$C(CH_3)_3$], 60.8 [$C(CH_3)_3$], 61.2 (NCH), 61.3, 62.4, and 62.9 ($3OCH_2$), 98.6 ($N_2C{=}C$), 110.0 and 146.3 (2CH), 150.6 and 152.3 (2C), 160.0 and 162.1 (2C=O), 163.6 (CH), 164.0 and 168.3 (2C=O).

4.2.12. Diethyl 2-[(2-ethoxy-2-oxoacetyl)(1,1,3,3-tetramethylbutyl)amino]-4*H*-pyrimido[1,2-*a*]pyrimidine-3,4-dicarboxylate (6e). Yellow crystals, mp 95 °C, yield: 0.40 g, 79%. IR (KBr) (ν_{max}/cm^{-1}): 1745, 1736, 1728, and 1668 (C=O), 1620, 1572, 1493, 1396, 1377, 1286, 1246, 1213, 1119, 1090, 1022, 797. MS, *m*/*z* (%): 504 (M^+, 3), 433 (20), 393 (17), 331 (62), 319 (100), 245 (26), 219 (70), 191 (21), 147 (12), 122 (34), 79 (35), 57 (20). Anal. Calcd for $C_{25}H_{36}N_4O_7$ (504.58): C, 59.51; H, 7.19; N, 11.10. Found: C, 59.7, H, 7.3; N, 10.9%. ^{1}H NMR (300.1 MHz, $CDCl_3$): δ 1.03 [9H, s, $C(CH_3)_3$], 1.19, 1.23, and 1.32 (9H, 3t, J=7.1 Hz, $3OCH_2CH_3$), 1.53 and 1.77 [6H, 2s, $C(CH_3)_2$], 2.17 and 2.38 (2H, 2d, AB system, ^2J=14.4 Hz, CH_AH_B), 4.03–4.35 (6H, m, $3OCH_2CH_3$), 5.89 (1H, s, NCH), 6.66 (1H, dd, J=6.6, 4.0 Hz, CH), 7.72 (1H, dd, J=6.6, 2.2 Hz, CH), 8.68 (1H, dd, J=4.0, 2.2 Hz, CH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 13.7, 13.9, and 14.4 ($3OCH_2CH_3$), 27.4 and 28.4 [$C(CH_3)_2$], 31.5 (CH_2), 31.7 [$C(CH_3)_3$], 31.8 [$C(CH_3)_3$], 61.2 (OCH_2), 61.4 (NCH), 62.4 and 62.9 ($2OCH_2$), 66.1 [$NC(CH_3)_2$], 99.1 ($N_2C{=}C$), 109.8 and 146.1 (2CH), 151.0 and 152.1 (2C), 159.8 and 162.1 (2C=O), 163.6 (CH), 164.0 and 168.4 (2C=O).

4.2.13. Dimethyl 2-[cyclohexyl(2-ethoxy-2-oxoacetyl)-amino]-4*H*-pyrazino[1,2-*a*]pyrimidine-3,4-dicarboxylate (6f). Orange crystals, mp 148 °C, yield: 0.41 g, 91%. IR (KBr) (ν_{max}/cm^{-1}): 1749, 1738, 1678, and 1662 (C=O), 1614, 1557, 1481, 1431, 1414, 1335, 1290, 1230, 1204, 1132, 1092, 1055, 1012, 916, 808, 735. MS, *m*/*z* (%): 446 (M^+, 2), 401 (83), 373 (7), 319 (45), 301 (11), 245 (55), 220 (100), 173 (13), 83 (16), 55 (14). Anal. Calcd for $C_{21}H_{26}N_4O_7$ (446.46): C, 56.50; H, 5.87; N, 12.55. Found: C, 56.5; H, 5.9; N, 12.4%. ^{1}H NMR (300.1 MHz, $CDCl_3$): δ 1.02–2.13 [3H, t, J=7.1 Hz, OCH_2CH_3; 10H, m, $CH(CH_2)_5$], 3.67 and 3.71 (6H, 2s, $2OCH_3$), 4.01–4.29 [3H, m, OCH_2CH_3 and $NCH(CH_2)_5$], 6.02 (1H, s, NCH), 7.23 (1H, d, J=4.1 Hz, CH), 7.81 (1H, d, J=4.1 Hz, CH), 8.54 (1H, s, CH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 12.4 (OCH_2CH_3), 24.0, 24.5, 24.6, 27.2, and 30.4 ($5CH_2$), 50.6 and 51.8 ($2OCH_3$), 55.5 [$NCH(CH_2)_5$], 59.6 (NCH), 60.3 (OCH_2), 88.4 ($N_2C{=}C$), 125.9 and 130.1 (2CH), 144.0 (C), 149.2 (CH), 151.4 (C), 160.0, 160.7, 162.8, and 166.0 (4C=O).

4.2.14. Diethyl 2-[cyclohexyl(2-ethoxy-2-oxoacetyl)-amino]-4*H*-pyrazino[1,2-*a*]pyrimidine-3,4-dicarboxylate (6g). Orange crystals, mp 125 °C, yield: 0.42 g, 89%.

IR (KBr) (ν_{max}/cm^{-1}): 1744, 1680, and 1659 (C=O), 1618, 1574, 1506, 1414, 1377, 1323, 1238, 1138, 1103, 1010. MS, *m*/*z* (%): 474 (M^+, 5), 401 (87), 373 (7), 319 (44), 301 (13), 245 (65), 220 (100), 173 (11), 83 (18), 55 (9). Anal. Calcd for $C_{23}H_{30}N_4O_7$ (474.51): C, 58.22; H, 6.37; N, 11.81. Found: C, 58.2; H, 6.4; N, 11.7%. ^{1}H NMR (300.1 MHz, $CDCl_3$): δ 1.03–2.04 [9H, 3t, J=7.1 Hz, $3OCH_2CH_3$; 10H, m, $CH(CH_2)_5$], 4.00–4.35 [7H, m, $3OCH_2CH_3$ and $NCH(CH_2)_5$], 5.99 (1H, s, NCH), 7.20 (1H, d, J=4.0 Hz, CH), 7.76 (1H, d, J=4.0 Hz, CH), 8.51 (1H, s, CH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 12.3, 12.4, and 12.6 ($3OCH_2CH_3$), 24.0, 24.5, 24.6, 27.2, and 30.5 ($5CH_2$), 55.3 [$NCH(CH_2)_5$], 59.5 (OCH_2), 59.8 (NCH), 60.3 and 61.2 ($2OCH_2$), 90.1 ($N_2C=C$), 125.9 and 129.5 (2CH), 143.9 (C), 149.2 (CH), 150.6 (C), 159.8, 160.6, 162.6, and 165.5 (4C=O).

Acknowledgements

This research was supported by the Research Council of the University of Tehran as research project (6102036/1/02).

References and notes

1. (a) *Multicomponent Reactions*; Zhu, J., Bienaymé, H., Eds.; Wiley: Weinheim, 2005; (b) Dömling, A. *Chem. Rev.* **2006**, *106*, 17–89; (c) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3169–3210.
2. Hermecz, I.; Vasvári-Debreczy, L.; Mátyus, P. *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. V. F., Eds.; Pergamon: London, 1996; Chapter 8.23, pp 563–595 and references therein.
3. Vasvári-Debreczy, L.; Hermecz, I.; Mátyus, P. *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. V. F., Eds.; Pergamon: London, 1996; Chapter 8.25, pp 633–706 and references therein.
4. (a) The first part of this paper has been published as a preliminary form: Adib, M.; Sayahi, M. H.; Nosrati, M.; Zhu, L.-G. *Tetrahedron Lett.* **2007**, *48*, 4195–4198; (b) Adib, M.; Yavari, H.; Mollahosseini, M. *Tetrahedron Lett.* **2004**, *45*, 1803–1805.
5. Kappe, C. O.; Kappe, T. *Arch. Pharm.* **1991**, *324*, 863–866.
6. Lennig, P.; Stengelin, S.; Klabunde, T.; Gossel, M.; Safar, P.; Smrcina, M.; Spoonamore, J.; Merriman, G.; Klein, J. T.; Whiteley, B.; Lanter C.; Bordeau, K.; Yang, Z. PCT Int. Appl. 2006, WO 2006, 24390; *Chem. Abstr.* **2006**, *144*, 274545g.
7. Eynde, J. J. V.; Hecq, N.; Kataeva, O.; Kappe, C. O. *Tetrahedron* **2001**, *57*, 1785–1791.
8. Pratap, R.; Kushwaha, S. P.; Goel, A.; Ram, V. J. *Tetrahedron Lett.* **2007**, *48*, 549–553.
9. Adib, M.; Sheibani, E.; Mostofi, M.; Ghanbary, K.; Bijanzadeh, H. R. *Tetrahedron* **2006**, *62*, 3435–3438; Adib, M.; Tahermansouri, H.; Aali Koloogani, S.; Mohammadi, B.; Bijanzadeh, H. R. *Tetrahedron Lett.* **2006**, *47*, 5957–5960; Adib, M.; Mahdavi, M.; Mahmoodi, N.; Pirelahi, H.; Bijanzadeh, H. R. *Synlett* **2006**, 1765–1767; Adib, M.; Haghighat Jahromi, A.; Tavoosi, N.; Mahdavi, M.; Bijanzadeh, H. R. *Tetrahedron Lett.* **2006**, *47*, 2965–2967; Adib, M.; Ghanbary, K.; Mostofi, M.; Bijanzadeh, H. R. *Tetrahedron* **2005**, *61*, 2645–2648.
10. *Selected X-ray crystallographic data for compound* **4a**: $C_{22}H_{27}N_3O_7$, triclinic, space group=$P\bar{1}$ (No. 2), a=11.353(2) Å, b=13.700(3) Å, c=15.132(3) Å, V=2245.1(7) Å3, T=295(2) K, Z=4, D_{calcd}=1.318 g cm^{-3}, μ (Mo Kα)=0.099 mm^{-1}, 17,002 reflections measured, 8265 unique reflections (R_{int}=0.0705), 4016 observed reflections, final R_1=0.074, wR_2=0.150 and for all data R_1=0.158, wR_2=0.188. CCDC 636589 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
11. Ugi, I. *Isonitrile Chemistry*; Academic: London, 1971; Ugi, I. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 810–819; Walborsky, H. M.; Periasamy, M. P. *The Chemistry of Functional Groups, Supplement C*; Patai, S., Rappaport, Z., Eds.; Wiley: New York, NY, 1983; Chapter 8.20, pp 835–837; Nair, V.; Vinod, A. U.; Nair, J. S.; Sreekanth, A. R.; Rath, N. P. *Tetrahedron Lett.* **2000**, *41*, 6675–6679; Nair, V.; Deepthi, A. *Tetrahedron Lett.* **2006**, *47*, 2037–2039.
12. To a magnetically stirred solution of the appropriate acyl chloride (ethyl chloroglyoxalate or ethyl chloroformate) (0.01 mol) in dry CH_2Cl_2 (60 mL) was added a solution of the appropriate amine (0.02 mol) in a minimum volume of dry CH_2Cl_2 at −5 °C over 2–3 min. The reaction mixture was stirred for 15 min and then warmed up to room temperature and stirred for 2 h. Then, the solvent was evaporated to 20 mL. The chloride salt was separated by suction and filtration. The filtrate was washed with water (2×30 mL) and dried over anhydrous sodium sulfate. The solvent was removed and the *N*-(2-heteroaryl)amide was obtained as colorless crystals.