An efficient route for the synthesis of a new class of pyrido[2,3-*d*]pyrimidine derivatives†

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Received 30th November 2006, Accepted 13th March 2007
First published as an Advance Article on the web 28th March 2007
DOI: 10.1039/b617201f

A new reaction of 4-arylidene-3-methylisoxazol-5(4*H*)-one or 4-arylidene-2-phenyloxazol-5(4*H*)-one with 2,6-diaminopyrimidin-4(3*H*)-one is described and a number of new pyrido[2,3-*d*]pyrimidine-4,7-dione derivatives are synthesized. This protocol has the advantages of good yields, broad substrate scope and simple work-up.

Introduction

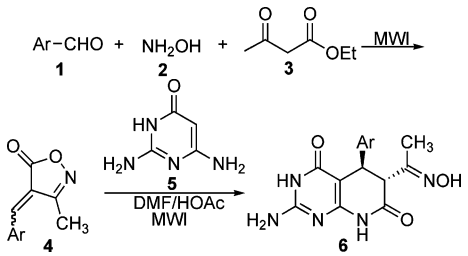
For small organic molecules, simple nitrogen-containing heterocycles receive a large amount of attention in the literature, as a consequence of their exciting biological properties and their role as pharmacophores of considerable historical importance. Of these heterocycles, the synthesis, reactions and biological activities of pyridine containing molecules stands as an ever expanding area of research in heteroaromatic chemistry and this structural motif appears in a large number of pharmaceutical agents and natural products.[1]

Pyrido[2,3-*d*]pyrimidine systems are of great interest because of their dihydrofolate reductase inhibiting, anticancer,[2–4] antiviral,[5,6] anti-inflammatory[7] and insecticidal activity.[8] Due to their diverse range of biological properties, interest in pyrido[2,3-*d*]pyrimidine derivatives has increased dramatically in recent years, and numerous efforts have been directed towards the preparation of pyrido[2,3-*d*]pyrimidines. Studies indicated that various substituents in different positions of the pyridine or pyrimidine ring display different biological and pharmacological activities.[9–15] To the best of our knowledge, however, the pyrido[2,3-*d*]pyrimidine-4,7-dione with a hydroxyiminoethyl or benzamido group in the 6-position has seldom been investigated.

In the context of our long-standing interest[16] in the design and development of heterocyclic compounds of biological importance and to expand the libraries of pyrido[2,3-*d*]pyrimidine for biomedical screening, we herein report a novel and efficient route for the synthesis of a new type of pyrido[2,3-*d*]pyrimidine-4,7-dione derivatives.

Result and discussion

The starting material 4-arylidene-3-methylisoxazol-5(4*H*)-ones **4** were easily obtained by the reaction of aldehyde **1**, hydroxylamine **2**, and ethyl acetoacetate **3** under microwave irradiation (MWI). Treatment of **4** with an equimolar amount of commercially available 2,6-diaminopyrimidin-4(3*H*)-one **5** in the presence of DMF and acetic acid under MWI afforded the target compound 2-amino-6-(1-hydroxyiminoethyl)-5,6-dihydro-5-arylpyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione **6** in excellent yield (Scheme 1).



Scheme 1

In order to optimize the reaction conditions, different organic solvents, such as ethanol, glycol, acetic acid, DMF and mixed DMF–HOAc (HOAc acts as both solvent and catalyst) were tested in the synthesis of **6a** at 90 °C. Table 1 shows that the reactions in mixed DMF–HOAc (preferred volume ratio: 2 : 1) gave the best results (entry 7 of Table 1).

Moreover, to further optimize the reaction temperature, reactions using 4-(4-fluorobenzylidene)-3-methylisoxazol-5(4*H*)-one **4a** and **5** were carried out in the range of 90 to 160 °C in increments of 10 °C each time in mixed DMF–HOAc (volume ratio: 2 : 1) under microwave irradiation (initial power 150 W, maximum power 240 W). The results are shown in Table 2. When the temperature was increased from 90 °C to 140 °C, the yield of product **6a** was improved. However, no significant increase in the yield of product **6a** was observed as the reaction temperature

Table 1 Solvent optimization for the synthesis of **6a** at 90 °C under MWI

Entry	Solvent	Time/min	Yield (%)
1	EtOH	12	26
2	Glycol	10	40
3	HOAc	9	44
4	DMF	9	41
5	DMF–HOAc (4 : 1)[a]	8	48
6	DMF–HOAc (3 : 1)[a]	8	51
7	DMF–HOAc (2 : 1)[a]	8	61
8	DMF–HOAc (1 : 1)[a]	8	53

[a] Volume ratio.

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† Electronic supplementary information (ESI) available: Characterization data for compounds **6a–n** and **8a–h** and **10a–i**. See DOI: 10.1039/b617201f

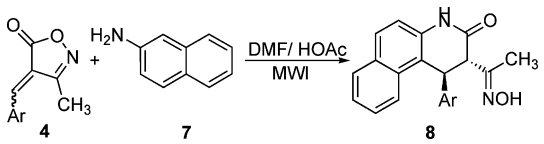
Table 2 Temperature optimization for the synthesis of **6a** under MWI

Entry	T/°C	Time/min	Yield (%)
1	90	8	61
2	100	8	64
3	110	8	71
4	120	8	78
5	130	7	82
6	140	7	89
7	150	7	83
8	160	7	80

was raised from 140 °C to 160 °C. Therefore, the temperature of 140 °C was chosen for all further microwave-assisted reactions

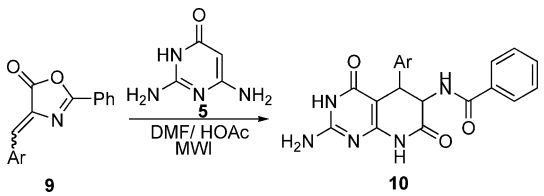
Under these optimized conditions [140 °C, DMF–HOAc (2 : 1)], a series of new type of pyrido[2,3-*d*]pyrimidine-4,7-dione derivatives were synthesized *via* reactions of **4** and **5** under microwave irradiation (Table 3, entries 1–14). In order to examine the applicability of this cascade reaction, we employed naphthalen-2-amine **7** instead of **5** to react with **4** in similar conditions (Scheme 2). The reaction proceeded smoothly. To our delight, a series of compounds **8** were obtained in good yields (Table 3, entries 15–22).

To further expand the scope of the application of this cascade reaction and enlarge the libraries of pyrido[2,3-*d*]pyrimidine-4,7-diones, the 4-arylidene-2-phenyl-5(4*H*)-oxazolones **9**, which were conveniently prepared according to our reported procedure,[17] were employed instead of **4** as precursor to synthesize another



Scheme 2

new type of pyrido[2,3-*d*]pyrimidine-4,7-dione derivatives. To our delight, the reaction of **5** and **9** proceeded smoothly under the aforementioned conditions and gave a series of *N*-(2-amino-4,7-dioxo-5-aryl-3,4,5,6,7,8-hexahydropyrido[2,3-*d*]pyrimidin-6-yl)-benzamides **10** (Scheme 3) in good yields (Table 3, entries 23–31).



Scheme 3

All the products were characterized by IR, ^{1}H NMR spectra and elemental analyses. The structure of **8e** was also determined by X-ray crystallography (Fig. 1).[18]

Regarding the structure of **8** the assignment of **8e** is described. ^{1}H NMR showed two singlets at δ 5.21 (s, 1H, CH), 4.22 (s, 1H, CH) assigned to C2 and C3 (Fig. 1). Calculation based on the

Table 3 Synthesis of products **6**, **8** and **10** under MWI

Entry	Product	**5** or **7**	**4** or **9**	Ar	Time/min	Yield[a] (%)	Mp/°C
1	**6a**	**5**	**4a**	4-FC_6H_4	7	89	256–258
2	**6b**	**5**	**4b**	4-ClC_6H_4	7	87	274–276
3	**6c**	**5**	**4c**	4-BrC_6H_4	7	85	278–280
4	**6d**	**5**	**4d**	2,4-$Cl_2C_6H_3$	8	89	286–288
5	**6e**	**5**	**4e**	2-ClC_6H_4	7	78	252–254
6	**6f**	**5**	**4f**	3-$NO_2C_6H_4$	8	83	285–286
7	**6g**	**5**	**4g**	C_6H_5	9	89	260–262
8	**6h**	**5**	**4h**	3,4-$(CH_3O)_2C_6H_3$	8	87	243–244
9	**6i**	**5**	**4i**	3,4,5-$(CH_3O)_3C_6H_2$	10	83	245–246
10	**6j**	**5**	**4j**	4-$CH_3OC_6H_4$	8	88	256–258
11	**6k**	**5**	**4k**	4-OH-3-$NO_2C_6H_3$	7	82	>300
12	**6l**	**5**	**4l**	4-$CH_3C_6H_4$	8	90	255–257
13	**6m**	**5**	**4m**	3,4-$(OCH_2O)C_6H_3$	9	89	270–271
14	**6n**	**5**	**4n**	2-Thienyl	10	78	258–259
15	**8a**	**7**	**4b**	4-ClC_6H_4	7	86	220–221
16	**8b**	**7**	**4c**	4-BrC_6H_4	7	87	229–231
17	**8c**	**7**	**4d**	2,4-$Cl_2C_6H_3$	6	85	250–252
18	**8d**	**7**	**4e**	2-ClC_6H_4	8	81	268–270
19	**8e**	**7**	**4f**	3-$NO_2C_6H_4$	6	82	246–248
20	**8f**	**7**	**4g**	C_6H_5	8	80	250–252
21	**8g**	**7**	**4h**	3,4-$(OCH_3)_2C_6H_3$	8	81	248–250
22	**8h**	**7**	**4l**	4-$CH_3C_6H_4$	7	76	245–247
23	**10a**	**5**	**9a**	4-FC_6H_4	7	91	>300
24	**10b**	**5**	**9b**	4-ClC_6H_4	7	90	>300
25	**10c**	**5**	**9c**	4-BrC_6H_4	6	89	>300
26	**10d**	**5**	**9d**	2,4-$Cl_2C_6H_3$	7	88	>300
27	**10e**	**5**	**9e**	3,4-$Cl_2C_6H_3$	7	88	>300
28	**10f**	**5**	**9f**	4-$NO_2C_6H_4$	6	86	>300
29	**10g**	**5**	**9g**	3,4-$(CH_3O)_2C_6H_3$	9	83	>300
30	**10h**	**5**	**9h**	4-$CH_3OC_6H_4$	8	89	>300
31	**10i**	**5**	**9i**	4-OH-3-$NO_2C_6H_3$	6	85	>300

[a] Isolated yields.

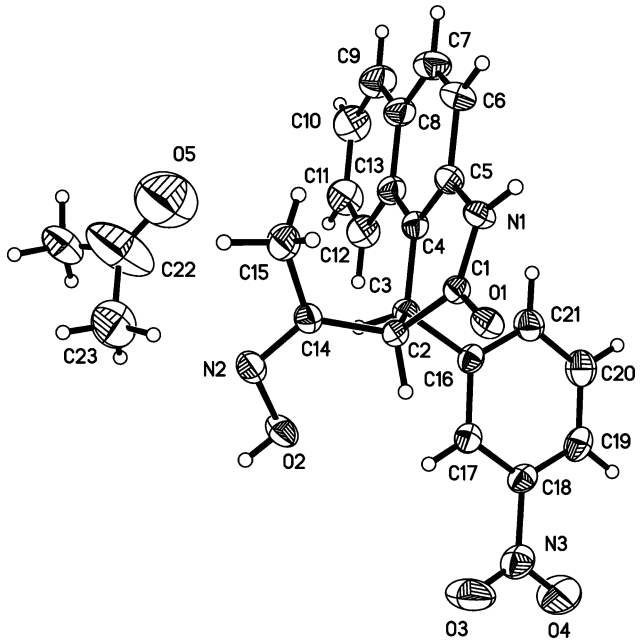
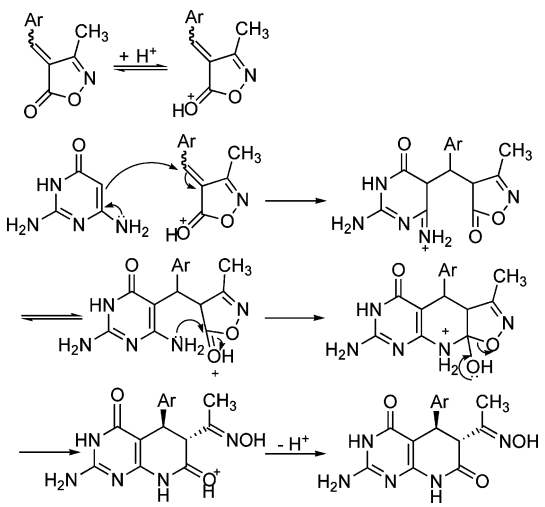


Fig. 1 ORTEP diagram of **8e**.

crystal data of **8e** showed that the torsion angle of H2–C2–C3–H3 is 80.10° which explains why the coupling constants of C2–H2 and C3–H3 cannot be measured. The reaction may give two possible diastereoisomers: *trans*-isomer and *cis*-isomer but only the *trans*-isomer was isolated. It is particularly noteworthy that the ^{1}H NMR spectrum of **6** also showed two singlets at δ 3.97–3.28 pm and δ 4.12–4.57 pm assigned to C5 and C6, respectively, a possible reason is similar to that of **8e**.

Although the detailed mechanism of the reaction has not been established in an experimental manner, the formation of **6** could be explained by a reaction sequence presented in Scheme 4. We propose that the reaction proceeds *via* a sequence of Michael addition, cyclization and ring opening. In this reaction, glacial acetic acid acts as both solvent and catalyst.



Scheme 4

Conclusion

In summary, we have developed a simple and efficient method for the synthesis of a series of new pyrido[2,3-*d*]pyrimidine-4,7-dione derivatives by a novel cascade reaction. This method has the advantages of shorter reaction time and higher yields as well as convenient operation. Most importantly, this series of pyrido[2,3-*d*]pyrimidine-4,7-dione derivatives may provide new classes of biologically active compounds for biomedical screening. An extension of this work is currently under investigation.

Experimental

All reactions were performed in a monomodal Emrys™ Creator from Personal Chemistry, Uppsala, Sweden. Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on an FT-IR-tensor 27 spectrometer. ^{1}H NMR spectra were measured on a DPX 400 MHz spectrometer using TMS as an internal standard and DMSO-d_6 as solvent. Elemental analysis was determined by using a Perkin-Elmer 240c elemental analysis instrument.

General procedure for the synthesis of compounds 6 with microwave irradiation

In a 10 mL reaction vial, the 4-arylidene-3-methylisoxazol-5(4*H*)-one **4** (1 mmol), 2,6-diamino-pyrimidin-4(3*H*)-one **5** (1 mmol), DMF and HOAc (2 mL) (2 : 1, V/V) were mixed and then capped. The mixture was irradiated at 240 W (initial power 150 W, maximum power 240 W) at 140 °C for a given time. The reaction mixture was cooled to room temperature and poured into water (50 mL), filtered to give the crude product, which was further purified by recrystallization from mixed DMF–EtOH to give pure 2-amino-6-(1-hydroxyiminoethyl)-5,6-dihydro-5-arylpyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione **6** (Table 3).

2-Amino-6-(1-hydroxyiminoethyl)-5-(4-fluorophenyl)-5,6-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione (6a)

IR (KBr ν, cm^{-1}): 3478, 3340, 3198, 2944, 1687, 1649, 1508, 1480, 1358, 1312, 816, 773, 622; ^{1}H NMR (DMSO-d_6) (δ, ppm): 10.84 (s, 1H, OH), 10.57 (s, 1H, NH), 10.23 (s, 1H, NH), 7.24–7.21 (m, 2H, ArH), 7.14–7.10 (m, 2H, ArH), 6.52 (br s, 2H, NH_2), 4.23 (s, 1H, CH), 3.30 (s, 1H, CH), 1.88 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6) (δ, ppm): 169.7, 161.7, 156. 6, 155.2, 151. 7, 143.7, 130.7, 129.5, 128.4, 90.2, 56.1, 35.8, 13.1; Anal. calcd for $C_{15}H_{14}FN_5O_3$: C, 54.38; H, 4.26; N, 21.14. Found: C, 54.15; H, 4.07; N, 21.44%.

General procedure for the synthesis of compounds 8 with microwave irradiation

In a 10 mL reaction vial, the 4-arylidene-3-methylisoxazol-5(4*H*)-one **4** (1 mmol), naphthalen-2-amine **7** (1 mmol), DMF and HOAc (2 mL) (2 : 1, V/V) were mixed and then capped. The mixture was irradiated at 240 W (initial power 150 W, maximum power 240 W) at 140 °C for a given time. The reaction mixture was cooled to room temperature and poured into water (50 mL), filtered to give the crude product, which was further purified by recrystallization from

mixed DMF–EtOH to give pure 1-aryl-2-(1-hydroxyiminoethyl)-1,2,3,4-tetrahydro-3-oxobenzo[*f*]quinolines **8** (Table 3).

1-(3-Nitrophenyl)-2-(1-hydroxyiminoethyl)-1,2,3,4-tetrahydro-3-oxobenzo[*f*]quinolines (8e)

IR (KBr ν, cm^{-1}): 3364, 3234, 3041, 2943, 2861, 1674, 1541, 1431, 844, 765, 647; ^{1}H NMR (DMSO-d_6) (δ, ppm): 11.40 (s, 1H, OH), 11.04 (s, 1H, NH), 8.10 (d, 1H, ArH, J = 8.4 Hz), 8.00–7.90 (m, 3H, ArH), 7.72 (d, 1H, J = 8.4 Hz, ArH), 7.63 (t, 1H, ArH, J = 8.0 Hz), 7.54 (d, 1H, ArH, J = 7.6 Hz), 7.46–7.37 (m, 3H, ArH), 5.21 (s, 1H, CH), 4.22 (s, 1H, CH), 1.54 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6) (δ, ppm): 166.9, 152.0, 138.2, 136.3, 132.4, 131.1, 130.4, 129.4, 129.3, 129.0, 128.5, 128.0, 127.7, 126.8, 124.3, 121.9, 117.1, 115.1, 53.5, 37.2, 18.7; Anal. calcd for $C_{21}H_{17}N_3O_4$: C, 67.19; H, 4.56; N, 11.19. Found: C, 67.36; H, 4.35; N, 11.37%.

General procedure for the synthesis of compounds 10 with microwave irradiation

In a 10 mL reaction vial, the 4-arylidene-2-phenyl-5(4*H*)-oxazolone **9** (1 mmol), 2,6-diaminopyrimidin-4(3*H*)-one **5** (1 mmol), DMF and HOAc (2 mL) (2 : 1, v/v) were mixed and then capped. The mixture was irradiated at 240 W at 140 °C for a given time. The reaction mixture was cooled to room temperature and poured into water (50 mL), filtered to give the crude product, which was further purified by recrystallization from mixed DMF–EtOH to give pure *N*-(2-amino-4,7-dioxo-5-aryl-3,4,5,6,7,8-hexahydropyrido[2,3-*d*]pyrimidin-6-yl)benzamides **10** (Table 3).

N-(2-Amino-5-(4-fluorophenyl)-3,4,5,6,7,8-hexahydro-4,7-dioxopyrido[2,3-*d*]pyrimidin-6-yl)benzamide (10a)

IR (KBr ν, cm^{-1}): 3453, 3339, 3201, 2904, 1702, 1652, 1508, 1487, 1375, 874, 794, 705; ^{1}H NMR (DMSO-d_6) (δ, ppm): 10.72 (s, 1H, NH), 10.59 (s, 1H, NH), 7.83 (d, 1H, NH, J = 6.4 Hz), 7.75 (d, 2H, ArH, J = 8.0 Hz), 7.56–7.43 (m, 3H, ArH), 7.09–6.98 (m, 4H, ArH), 6.66 (br s, 2H, NH_2), 5.06 (t, 1H, CH, J = 7.2 Hz), 4.49 (d, 1H, CH, J = 7.6 Hz); ^{13}C NMR (DMSO-d_6) (δ, ppm): 169.3, 166.9, 161.5, 156.2, 155.5, 143.7, 133.9, 131.7, 131.1, 130.6, 128.8, 128.6, 127.3, 92.0, 54.0, 37.6; Anal. calcd for $C_{20}H_{16}FN_5O_3$: C, 61.07; H, 4.10; N, 17.80. Found: C, 61.21; H, 4.23; N, 17.95%.

Acknowledgements

We thank for the National Natural Science Foundation of China (Nos. 20372057 and 20672090), Natural Science Foundation of the Jiangsu Province (No. BK2006033) for financial support.

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17 S. J. Tu, H. Jiang, Q. Y. Zhuang, C. B. Miao, D. Q. Shi, X. S. Wang and Y. Gao, *Chin. J. Org. Chem.*, 2003, **23**, 491.
18 The singal-crystal growth was carried out in a mixed solvent of acetone and ethanol at room temperature. X-Ray crystallographic analysis was performed with a Siemens SMART CCD and a Semens P4 diffractometer (graphite monochromator, MoKa radiation λ = 0.71073 Å). The compound examined was an acetone solvate and there is a quarter of an acetone molecule per molecule of compound **8e**. Crystal data for **8e**: $C_{21.75}H_{18.50}N_3O_{4.25}$, colorless, crystal dimensions 0.40 × 0.35 × 0.09 mm, monoclinic, space group $C2/c$, a = 18.38 (2), b = 9.913 (12), c = 23.37 (3) Å, α = 90, β = 106.34 (2), γ = 90°, V = 4087 (8) Å^3, M_r = 389.90, Z = 8, D_c = 1.267 Mg m^{-3}, λ = 0.71073 Å, μ (Mo-Kα) = 0.090 mm^{-1}, $F(000)$ = 1632, S = 1.012, R_1 = 0.0641, wR_2 = 0.1565. CCDC reference number 629332. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b617201f.