Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 2745–2747

TETRAHEDRON LETTERS

Efficient synthesis of novel pyrido[3,2-*d*]pyrimidine-2,4-diones

R. Mamouni,[a] M. Aadil,[a] M. Akssira,[a,*] J. Lasri[b] and J. Sepulveda-Arques[b]

[a]*Laboratoire de Chimie Bioorganique et Analytique, Université Hassan II-Mohammedia, BP 146, 20650 Mohammedia, Morocco*
[b]*Departamento de Química Orgánica, Facultad de Farmacia, Universidad de Valencia, Avda. Vicent Andres Estelles s/n, 46180 Burjassot, Valencia, Spain*

Received 17 January 2003; revised 27 January 2003; accepted 28 January 2003

Abstract—A series of pyrido[3,2-*d*]pyrimidine-2,4-diones **5a**–**g** have been synthesized through conversion of 2,3-pyridinedicarboxylic anhydride **1** into half-ester **2**, subsequent Curtius rearrangement and further reaction with amino acids. © 2003 Elsevier Science Ltd. All rights reserved.

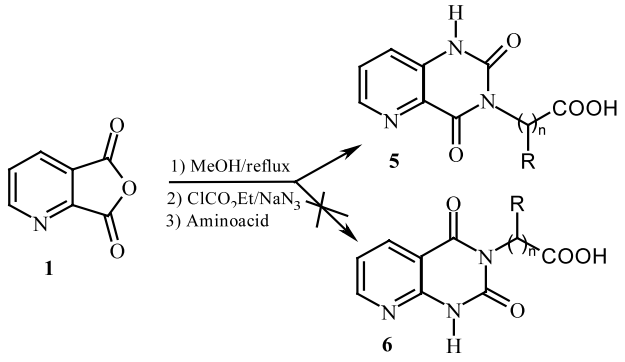
Pyridopyrimidine systems are of great interest because of its dihydrofolate reductase inhibiting, antibacterial,[1,2] antitumor[3] and antiepileptic activity,[4] and it has recently been reported that a number of compounds bearing the pyridopyrimidine moiety exhibited excellent PDE4 activity.[5,6] Thus, considerable attention has been focused on the development of new methodologies to synthesize many kinds of pyridopyrimidine systems.

We have shown previously that the phthalic and pyrazolic half-esters are versatile compounds for the synthesis of different fused heterocyclic systems with a potential therapeutic interest, such as, quinazoline-2,4-diones,[8] pyrazolo[3,4-*d*]pyrimidine-4,6-diones,[9] pyrazolo[4,3-*d*]pyrimidine-5,7-diones[9] and isomeric nitroquinazoline-2,4-diones.[10]

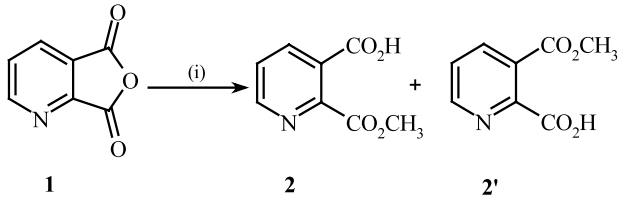
In our ongoing research program for new heterocycles containg quinazoline or pyrimidine ring systems, we report here a convenient synthesis of new pyrido[3,2-*d*]pyrimidines **5**. The synthesis of this type of molecules is hardly cited in the literature.

Recently, Romerosa et al.[11] reported the synthesis of pyrido[2,3-*d*]pyrimidinediones **6** through a sequence of reactions that involve the methanolysis of pyridine-2,3-dicarboxylic anhydride. Repeating this experiment, we have demonstrated that structures were erroneously assigned and we show that the compounds obtained through of the synthetic procedure were pyrido[3,2-*d*]pyrimidinediones **5** (Scheme 1).

The preparation of 2,3-pyridinedicarboxylic acid methyl ester has been notably investigated.[12] In our hands, according to the previous report,[13] the esterification of pyridine-2,3-dicarboxylic anhydride **1** by methanol afforded a mixture of **2** (stable isomer) as a major product with variable quantities of **2′** (labile isomer) (Scheme 2). The 2,3-pyridinecarboxylic acid 2-methyl ester **2** was isolated as a pure compound without difficulty by Kenyon and Takers procedure.[12]



Scheme 1.



Scheme 2. *Reagents and conditions*: (i) MeOH/reflux.

* Corresponding author. Fax: +212-23315353; e-mail: akssira@uh2m.ac.ma

0040-4039/03/$ - see front matter © 2003 Elsevier Science Ltd. All rights reserved.
doi:10.1016/S0040-4039(03)00273-9

Treatment of mono-ester **2** by ethyl chloroformate with triethylamine and sodium azide in the presence of a small amount of water gave the azide **3** which was transformed by Curtius rearrangement into isocyanate **4**. The subsequent reaction of isocyanate **4** with a series of amino acids under mild conditions by gentle heating (around 50°C) led to pyrido[3,2-*d*]pyrimidinediones **5a**–**g**[14] in good yields (Scheme 3, Table 1).

Confirmation of the structure of compounds **5**, as pyrido[3,2-*d*]pyrimidine systems was established with NMR two-dimensional experiments.[15] The HMBC experiment carried out with compound **5a** showed the long-range correlations of three and/or two bonds between carbons and protons, and the relative spatial distances of protons.

The structure of compound **5a** agree with the long-range C, H correlations observed in HMBC (Fig. 1).

The spectrum data reveal the correlation contours between the NH proton and C8 signals, the NH proton and C4a signals, the H6 and C8 signals, the H6 and C4a signals, the H8 and C4a signals, H8 and C6 signals and the H7 and C8a signals, served to determine the position of NH in relation to N of the pyridine.

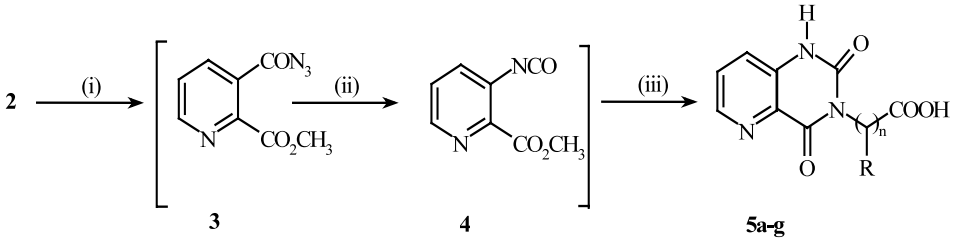
Table 1. Synthesis of pyrido[3,2-*d*]pyrimidine-2,4-diones

Amino acids	R	*n*	Product (yield%)	Mp (°C)
Glycine	H	1	**5a** (85)	329–330
β-Alanine	H	2	**5b** (65)	302–303
L-Alanine	CH_3	1	**5c** (80)	228–229
DL-Alanine	CH_3	1	**5d** (82)	328–330
L-Phenylalanine	CH_2Ph	1	**5e** (75)	269–271
L-Phenylglycine	Ph	1	**5f** (94)	300–302
L-Glutamic acid	$(CH_2)_2COOH$	1	**5g** (88)	290–291

The remaining NOE (Fig. 2) together with H, H couplings, were in agreement with the structure of **5a**.

Selective low power irradiation of the NH proton and H6 provides signal enhancement respectively of H8 and H7. Irradiation of the H8 provide signal enhancement of the NH proton and H7.

The structure of **5a** (and also the other compounds prepared) has been determined unambiguously as 3-substituted-1,2,3,4-tetrahydro[3,2-*d*]pyrimidine-2,4-dione ring systems.



Scheme 3. *Reagents and conditions*: (i) (a) $ClCO_2Et$, Et_3N, THF, −10°C, (b) NaN_3, H_2O, −10°C; (ii) toluene, reflux; (c) amino acid, NaOH (1N), H_2O.

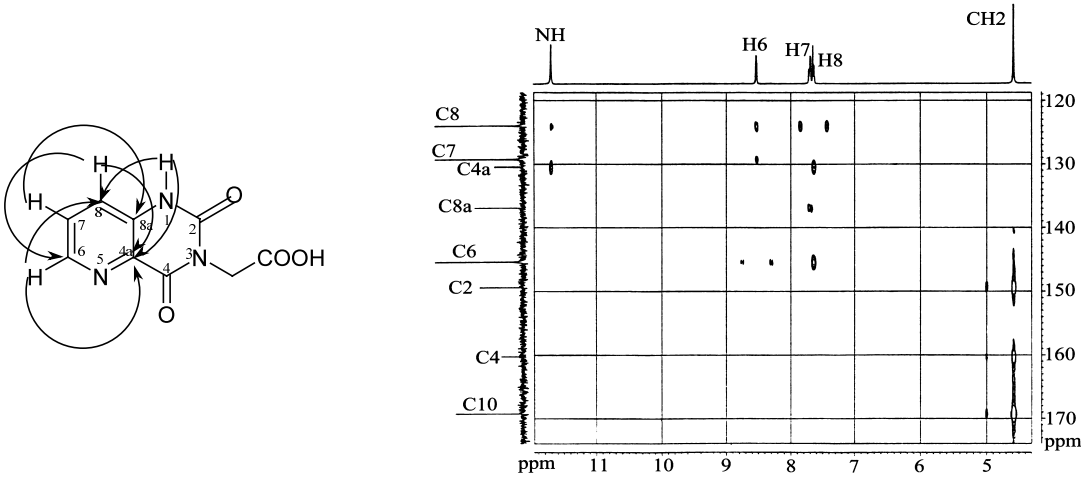


Figure 1. Portion of the HMBC spectrum of **5a** recorded in DMSO-d_6 at observation frequencies of 400/100 MHz for ^1H and ^{13}C NMR, respectively.

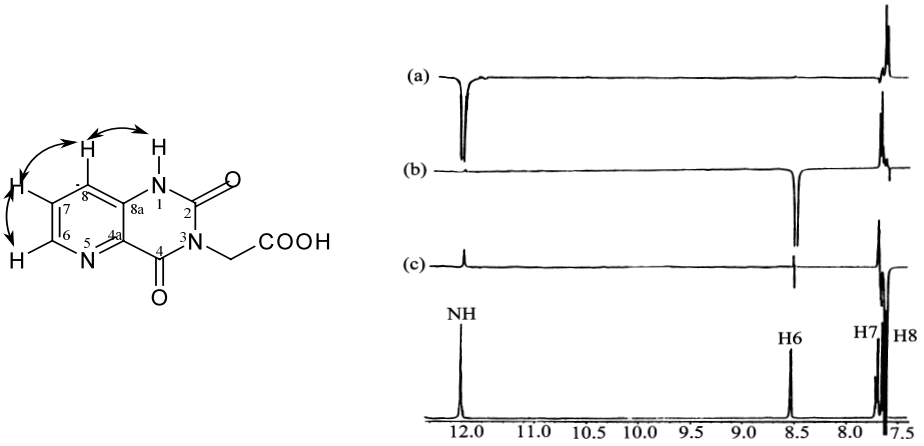


Figure 2. 400 MHz ^{1}H NMR spectrum of **5a** in DMSO-d_6; NOE difference spectra resulting from irradiation of (a) NH proton, (b) H6 and (c) H8.

In conclusion, this work presents a new synthesis of pyrido[3,2-*d*]pyrimidine-2,4-diones **5** through a short and efficient route, using 2,3-pyridinedicarboxylic acid as inexpensive starting material. We are currently exploring the construction of the other fused heterocyclic systems with the aim to determine a common pharmacophore.

Acknowledgements

The authors would like to acknowledge the financial support provided by the ministry ESRSFC of the Moroccan Government (PROTARS P2T2/07) and Mr. Haidour Ali from University of GRANADA, Spain (Centro de Instrumentación Científica), for carrying out NMR 2D experiences.

References

1. Hurlbert, B. S.; Valenti, B. F. *J. Med. Chem.* **1968**, *11*, 708.
2. Matsumoto, J.; Miinami, S. *J. Med. Chem.* **1975**, *18*, 74.
3. Griwsky, E. M.; Lee, S.; Sigel, C. W.; Duch, D. S.; Nickol, C. A. *J. Med. Chem.* **1980**, *23*, 327.
4. Bornschein, L.; Kraft, R.; Pfeifer, S.; Ullmann, M.; Longer, H. *Pharmazie* **1979**, *34*, 732.
5. (a) Alvarez, R.; Wilhem, R. S.; Shelton, E. R.; Daniels, D. V.; Yang, D.; Kelly, K.; Eglen, R. M. *Can. J. Physiol. Pharmacol.* **1994**, *72*, 510; (b) Wilhelm R. S.; Chin, R. L.; Devens, B. H.; Alverez, R. Int. Pat. Appl. WO 9,319,068; *Chem. Abstr.* **1994**, *122*, 164123.
6. Lowe, J. A., III; Archer, R. L.; Chapin, D. S.; Cheng, J. B.; Helweg, D.; Johnson, J. L.; Koe, B. K.; Lebel, L. A.; Moore, P. F.; Nielson, J. A.; Russo, L. L.; Shirley, J. T. *J. Med. Chem.* **1991**, *34*, 624.
8. Akssira, M.; Dahdouh, A.; Kasmi, H.; Boumzebra, M.; Canonne, P. *Heterocycles* **1993**, *36*, 1305.
9. El Haddad, M.; Soukri, M.; Lazar, S.; Bennamara, A.; Guillaumet, G.; Akssira, M. *J. Heterocyclic Chem.* **2000**, *37*, 1247 and references cited herein.
10. Aziane, D.; Soukri, M.; El Hakmaoui, A.; Lazar, S.; Essassi, M.; Guillaumet, G.; Akssira, M. *J. Heterocyclic Chem.* **2002**, *39*, 271.
11. Saoud, M.; Benabdelouahab, F. B.; El Guemmout, F.; Romerosa, A. M. *Heterocyclic Commun.* **2001**, *7*, 5.
12. Kenyon, J.; Thaker, K. *J. Chem. Soc.* **1957**, 2531.
13. Blanco, M. M.; Perillo, I. A.; Schapira, C. B. *J. Heterocyclic Chem.* **1999**, *36*, 979.
14. Compound **5a**: ^{1}H NMR (DMSO-d_6): δ 4.59 (s, 2H, CH_2), 7.62–7.76 (m, 2H, H_{Py}), 8.51–8.57 (m, 1H, H_{Py}), 11.75 (s, 1H, NH), 13.1 (bs, 1H, COOH); MS: *m*/*z* 222 [M+1].
Compound **5b**: ^{1}H NMR (DMSO-d_6): δ 2.5 (t, 2H, CH_2COOH), 4.11 (t, 2H, CH_2N), 7.50–7.70 (m, 2H, H_{Py}), 8.40–8.60 (m, 1H, H_{Py}), 11.53 (s, 1H, NH), 12.34 (bs, 1H, COOH); MS: *m*/*z* 236 [M+1].
Compound **5c**: ^{1}H NMR (DMSO-d_6): δ 1.7 (d, 3H, CH_3), 5.54 (q, 1H, CH), 7.40–7.58 (m, 2H, H_{Py}), 8.60–8.70 (m, 1H, H_{Py}); MS: *m*/*z* 236 [M+1].
Compound **5d**: ^{1}H NMR (DMSO-d_6): δ 1.48 (d, 3H, CH_3), 5.4 (q, 1H, CH), 7.50–7.80 (m, 2H, H_{Py}), 8.40–8.60 (m, 1H, H_{Py}), 11.65 (s, 1H, NH), 12.66 (bs, 1H, COOH); MS: *m*/*z* 236 [M+1].
Compound **5e**: ^{1}H NMR (DMSO-d_6): δ 3.35–3.56 (m, 2H, CH_2), 5.68–80 (m, 1H, CH), 7.36–7.50 (m, 3H, H_{Ph}), 8.10–8.35 (m, 2H, H_{Py}), 8.68–8.76 (m, 1H, H_{Py}), 8.56 (s, 1H, NH); MS: *m*/*z* 312 [M+1].
Compound **5f**: ^{1}H NMR (DMSO-d_6): δ 6.70 (s, 1H, CHPh), 7.49–7.60 (m, 3H, H_{Ph}), 7.93–8.20 (m, 2H, H_{Py}), 8.58–8.62 (m, 1H, H_{Py}), 10.65 (s, 1H, NH); MS: *m*/*z* 298 [M+1].
Compound **5g**: ^{1}H NMR (D_2O): δ 3.02 (dd, 2H, CH_2CH_2COOH, J=6.40 Hz), 3.36 (dt, 2H, CH_2CH_2COOH, J=7.72 Hz), 5.80 (dd, 1H, CH, J=6.97), 7.98–8.15 (m, 2H, H_{Py}), 8.20–8.35 (m, 1H, H_{Py}), 8.65 (s, 1H, NH); MS: *m*/*z* 294 [M+1].
15. Lin, L.-Z.; Lin, L.-J.; Cordell, G. A.; Luo, S.-Q.; Jiang, H.-F. *Magn. Res. Chem.* **1992**, *30*, 1097 and references cited therein.